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(57) Abstract: There is provided a method to modulate the differentiation state of embryonic stem cells in culture by the providing

STEM CELL

The invention relates to a method to modulate the differentiation state of embryonic stem cells.

During mammalian development those cells that form part of the embryo up until the formation of the blastocyst are said to be totipotent (e.g. each cell has the developmental potential to form a complete embryo and all the cells required to support the growth and development of said embryo). During the formation of the blastocyst, the cells that comprise the inner cell mass are said to be pluripotential (e.g. each cell has the developmental potential to form a variety of tissues).

Embryonic stem cells (ES cells, those with pluripotentiality) may be principally derived from two embryonic sources. Cells isolated from the inner cell mass are termed embryonic stem (ES) cells. In the laboratory mouse, similar cells can be derived from the culture of primordial germ cells isolated from the mesenteries or genital ridges of days 8.5-12.5 *post coitum* embryos. These would ultimately differentiate into germ cells and are referred to as embryonic germ cells (EG cells). Each of these types of pluripotential cell has a similar developmental potential with respect to differentiation into alternate cell types, but possible differences in behaviour (eg with respect to imprinting) have led to these cells to be distinguished from one another. Hereinafter embryonic stem cells will encompass both these stem cell – types.

Typically ES cell cultures have well defined characteristics. These include, but are not limited to; maintenance in culture for at least 20 passages when maintained on fibroblast feeder layers; produce clusters of cells in culture referred to as embryoid bodies; the ability to differentiate into multiple cell types in monolayer culture; and express ES cell specific markers.

Until very recently, *in vitro* culture of human ES cells was not possible. The first indication that conditions may be determined which could allow the establishment of human ES cells in culture is described in WO96/22362. The application describes cell lines and growth conditions which allow the continuous proliferation of primate ES cells which exhibit a range of characteristics or markers which are associated with stem cells having pluripotent characteristics.

More recently Thomson *et al* (1998) have published conditions in which human ES cells can be established in culture. The above characteristics shown by primate ES cells are also shown by the human ES cell lines. In addition the human cell lines show high levels of telomerase activity, a characteristic of cells which have the ability to divide continuously in culture in an undifferentiated state. Another group (Reubinoff et. al., 2000) have also reported the derivation of human ES cells from human blastocysts. A third group (Shamblott et. al., 1998) have described EG cell derivation.

A feature of ES cells is that, in the presence of fibroblast feeder layers, they retain the ability to divide in an undifferentiated state for several generations. If the feeder layers are removed then the cells differentiate. The differentiation is often to neurones or muscle cells but the exact mechanism by which this occurs and its control remain unsolved. It would be desirable to have a reliable culture system which does not require the presence of fibroblast feeder cells but includes the addition of a factor(s) which maintain ES cells in an undifferentiated state. A prerequisite to the successful exploitation of ES cells in tissue engineering is to provide a reliable and defined cell culture system which can be used to control the differentiation of ES cells into a selected cell-type. The identification of gene targets involved in maintaining ES cells as ES cells and the identification of gene targets involved in differentiation will facilitate this objective.

We have identified a regulatory pathway involved in the mechanism by which ES cells are maintained as ES cells in culture and which also influences the differentiation of said cells in culture. The regulatory pathway comprises two families of genes referred to as *Notch* and *Wnt*.

The *Notch* gene is a *Drosophila* prototype for a family of homologues found in diverse species, encoding large, single-span, transmembrane receptors (reviewed in Weinmaster, 1997). Within the extracellular domain, located distally from the transmembrane region, are found multiple (10-36), tandem arrays of epidermal growth factor-like repeats (Wharton et al., 1985; Kopezynski et al., 1988). More proximally are found 3 cysteine-rich, Lin-12/Notch repeats and two conserved cysteine residues. The intracellular domain contains, from proximal to distal with respect to the transmembrane region, a subtransmembrane region (STR), six ankyrin repeats and a region rich in proline, glutamic acid, serine and threonine (PEST). The generic Notch structure is illustrated in Figure 1.

Wnt genes encode diffusible, extracellular signalling molecules of around 350-400 amino acids in length, defined by a characteristic pattern of conserved cysteine residues, along with other invariant amino acids (see http://www.stanford.edu/~rnusse/wntwindow.html.

In the 1970s, the *wingless* (*wg*[1]) mutation of *Drosophila melanogaster* was described, in which affected individuals showed aberrant wing and haltere development (Sharma, 1973; Sharma and Chopra, 1976). When the gene disrupted by this mutation was subsequently identified, the predicted 468aa peptide sequence exhibited remarkable similarity to that of a murine gene, *int-1* (Cabrera et al., 1987; Rijsewijk et al., 1987), including an identical pattern of 23 conserved cysteine residues. *int-1* had earlier been identified as a common integration site of the murine mammary tumour virus, and a likely cellular oncogene (Nusse and Varmus, 1982; van Ooyen and Nusse, 1984). Thus, the two prototypic members of the *Wnt* gene family were described. Since that time, numerous homologues of *wingless/int-1* have

been identified in divergent organisms, including *Caenorhabditis elegans*, *Drosophila melanogaster*, *Xenopus laevis*, chicken, mouse and humans (reviewed in Cadigan and Nusse, 1997; Wodarz and Nusse, 1998). Lower organisms appear to possess a limited repertoire of *Wnt* genes in comparison to higher organisms, presumably reflecting their lesser developmental complexity. Additionally, vertebrates appear to express multiple, closely related orthologues of certain *Wnt*s. The *Wnt* family is composed of more than 60 members, with 14 human homologues alone. Well-documented roles exist for *Wnt* signalling in a variety of developmental processes, including cell fate specification and patterning within the central nervous system.

Wnt ligands interact with membrane-bound receptors of the frizzled family, leading to activation of a cytoplasmic protein, Dishevelled. Dishevelled inhibits Notch activation (2) and also inhibits the activity of an Axin-APC-GSK-3b complex, promoting formation of a bipartite transcriptional activator comprising b-catenin and TCF (4). Wnt signalling may be antagonised by extracellular molecules that compete for Wnt binding, including frizzled related proteins (FRP), Wnt inhibitory factors (WIF), Dickkopf and Cerberus. Expression of *Wnt* target genes may also be regulated by other proteins that bind to and alter the function of TCF. CREB-Binding Protein (CBP) exhibits a mutually antagonistic binding affinity for TCF with b-catenin and converts TCF into a repressor of target genes (8). Additionally, Notch activation may induce transcriptional repression by TCF, even in the presence of b-catenin, through expression of the TLE class of putative target genes (5,7).

As a model system to test the involvement of *Notch* and *Wnt* genes in the differentiation of ES cells we have used embryonal carcinoma cells which are stem cells of teratocarcinomas. The stem cells of early embryos and the stem cells of teratocarcinomas have been demonstrated experimentally to be capable of substituting for one another in their respective roles. Thus, an embryonic stem cell introduced to a syngeneic host may give rise to a teratocarcinoma containing all of the elements that would be found in a spontaneous tumour of this type (Mintz et al

1978). Likewise, embryonal carcinoma cells derived from a spontaneous germ cell carcinoma may participate in embryonic development, and generate normal somatic tissue following injection into a blastocyst (Brinster 1974; Mintz and Illmensee 1975; Papaioannou et al 1975). This clearly demonstrates that murine EC cells may respond to developmental cues in an appropriate manner, and that their differentiation may provide information pertinent to normal embryogenesis. Similarly, human EC cells may provide an insight into the processes that regulate human development.

The TERA2 cell line was derived from a lung metastasis of a human teratocarcinoma in the mid 1970s (Fogh and Trempe, 1975). Morphologically, TERA2 cultures are quite divergent from the characteristic EC phenotype and display significant heterogeneity, suggesting that these cells undergo spontaneous differentiation (Andrews et al., 1980). However, a tumour containing both embryonal carcinoma cells and differentiated derivatives was produced following injection of TERA2 into a nude mouse host (Andrews et al., 1983a; Andrews et al., 1983b; Andrews et al., 1984). A cell line established from the EC component of this tumour, named NTERA2, closely resembled and maintained the characteristic EC phenotype in culture and, unlike the parent line, was able to produce teratocarcinoma in nude mice with high frequency (Andrews et al., 1983a; Andrews et al., 1983b; Andrews et al., 1984). Additionally, various subclones of NTERA2 exhibit the ability to differentiate extensively *in vitro* following treatment with chemical inducers (eg retinoic acid (RA), HMBA) (Andrews, 1984; Andrews et al., 1986).

The expression of human *Notch* homologues were examined in NTERA2 to determine their involvement in ES cell differentiation.

We have discovered that members of the *Notch* gene family, *Notch1*(Genbank accession number AF308602), *Notch2* (Genbank accession number NM_024408) and *Notch3* (Genbank accession number NM_000435) are expressed in EC cells and NTERA2 cells. *Notch1* expression was detected as a mRNA band of around 7Kb in both EC and differentiated cultures of NTERA2. *Notch3*, like *Notch1*, was

examined in EC cells. A transcript of around 8Kb was readily detected in all samples. The endoderm-specific *Notch4* (Genbank accession number XM_004207) was not.

All three *Notch* homologues expressed by NTERA2 showed altered transcription during differentiation in response to retinoic acid. In each case, however, these changes were modest and expression was evident in both EC and differentiated cultures. The role of the Notch pathway in directing EC/ES differentiation may thus depend to a greater extent on the level of signalling activation rather than the abundance of the receptors. In order to investigate this possibility, the expression of candidate ligands for Notch receptors were examined. For example, *dlk* (Genbank accession number U15979) was detected at high levels in EC cultures, but its expression was almost extinguished by 3 days following RA treatment. Low levels were also observed through 7 and 14 days post-RA. However, by 21 days, *dlk* was up-regulated to the level seen in EC cultures. These profound changes may reflect an important role for dlk and other DSL ligands in regulating EC/ES differentiation through altered Notch signalling activation. This data is suggestive that the *Notch* signalling pathway is involved in regulating EC cell differentiation and, by extrapolation, human ES cell differentiation.

A degenerate PCR strategy was used to investigate the possible expression of novel *Wnt* genes in the NTERA2 system. The expression of a single *Wnt* gene, *Wnt-13*, was detected in NTERA2. *Wnt-13* was absent in EC cells, but showed induction and subsequent up-regulation following both retinoic acid and HMBA treatment. Both of these agents bring about extensive differentiation of NTERA2, accompanied by the loss of typical human EC surface markers.

We have examined the expression of components of the *Wnt* pathway and of transcripts corresponding to other proteins known to interact with *Wnt* signalling in NTERA2 cells. These cells are a model system for aspects of human embryogenesis and differentiate extensively *in vitro* in response to chemical inducers. Among the

cell types produced following retinoic acid treatment are functional, post-mitotic, CNS neurons (1,6,17).

The modulation of the *Notch* and *Wnt* signalling pathways may facilitate manipulation of embryonic stem cell differentiation. The term modulation refers to either the maintenance of embryonic stem cells as embryonic stem cells or the facilitation of differentiation of embryonic stem cells along defined cell lineages.

According to an aspect of the invention there is provided a method to modulate the phenotype of an embryonic stem cell comprising contacting said cell with a ligand binding domain of a polypeptide wherein said domain binds its cognate receptor expressed by said cell to modulate said phenotype.

According to a further aspect of the invention there is provided a method to modulate the differentiation of an embryonic stem cell comprising:

i) providing a culture of embryonic stem cells;
ii) providing at least one ligand, or the active binding fragment thereof, capable of binding its cognate receptor polypeptide expressed by said embryonic stem cell;
iii) forming a culture comprising embryonic stem cells and said ligand; and
iv) growing said cell culture.

In a preferred method of the invention said ligand is encoded by a nucleic acid molecule selected from the group consisting of:

i) a nucleic acid molecule as represented in Figure 22;
ii) a nucleic acid molecule which hybridises to the nucleic acid in (i) and which encodes a ligand capable of binding a Wnt receptor; and
iii) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (i) and (ii) above.

In a preferred method of the invention said ligand is selected from the group consisting of: WNT 1; WNT 2, WNT 3; WNT 4; WNT 5A; WNT 6; WNT 7A; WNT 8B; WNT 10B; WNT 11; WNT 14; WNT 16.

In a further preferred method of the invention said ligand is WNT 13.

In an alternative preferred method of the invention said ligand is encoded by a nucleic acid molecule selected from the group consisting of:

i) a nucleic acid molecule as represented in Figures 2, 4, 5, 7, 10, 12, 14, 16, or 18.

ii) a nucleic acid molecule which hybridises to the nucleic acid in (i) and which encodes a ligand capable of modulating embryonic stem cell differentiation; and

iii) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (i) and (ii) above.

In a further preferred method of the invention said ligand is selected from the group represented by the amino acid sequences in Figures 3, 6, 8, 9, 11, 13, 15, 17, 19, or polypeptide variants thereof.

Polypeptide variants are polypeptide sequences having at least 75% identity with the polypeptide sequences as herein disclosed, or fragments and functionally equivalent polypeptides thereof. In one embodiment, the polypeptides have at least 85% identity, more preferably at least 90% identity, even more preferably at least 95% identity, still more preferably at least 97% identity, and most preferably at least 99% identity with the amino acid sequences illustrated herein.

In a further preferred method of the invention said cells are induced to differentiate by the addition of at least one agent selected from the group consisting of: retinoic acid; HMBA ; bone morphogenetic proteins ; bromodeoxyuridine; lithium; sonic hedgehog .

Optionally the inducing agent and the ligand are added simultaneously to a culture of embryonic stem cells. Alternatively, the ligand is added before addition of said inducing agent.

According to a further aspect of the invention there is provided a method for modulating the differentiation of embryonic stem cells comprising:

i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule as represented in Figures 2, 4, 5, 7, 10, 12, 14, 16, 18.

b) a nucleic acid molecule which hybridises to the nucleic acid in (ii) and which encodes a ligand capable of modulating embryonic stem cell differentiation; and

c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.

ii) forming a culture comprising the cell identified in (i) above with an embryonic stem cell; and

iii) growing said culture under conditions suitable for the maintenance and/or differentiation of said embryonic stem cell.

According to a yet further aspect of the invention there is provided a method for modulating the differentiation of embryonic stem cells comprising:

i) providing a cell transfected with a nucleic acid molecule selected from the group comprising:

    a) a nucleic acid molecule as represented by the sequence in Figure 22;

    b) a nucleic acid molecule which hybridises to the nucleic acid in (a) and which encodes a ligand capable of binding a Wnt receptor; and

    c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.

ii) forming a culture comprising a cell as identified in (i) above with an embryonic stem cell; and

iii) growing said culture under conditions suitable for the maintenance and/or differentiation of embryonic stem cells.

In a preferred method of the invention said cell expresses Wnt-13.

Optionally the cells expressing the ligand(s) are mixed with a culture of undifferentiated embryonic stem cells. This is followed by addition of the inducing agent (eg retinoic acid; HMBA, bone morphogenetic proteins; bromodeoxyuridine; lithium; sonic hedgehog).

In a preferred method of the invention said nucleic acid molecule hybridises under stringent hybridisation conditions to the nucleic acid molecules represented in (a), (b) or (c) above.

Stringent hybridisation or washing conditions are well known in the art. For example, nucleic acid hybrids that are stable after washing in 0.1xSSC, 0.1% SDS at 60°C. It is well known in the art that optimal hybridisation conditions can be calculated if the sequence of the nucleic acid is known. For example, hybridisation conditions can be determined by the GC content of the nucleic acid subject to hybridisation. Please see Sambrook *et al* (1989) Molecular Cloning; A Laboratory Approach. A common formula for calculating the stringency conditions required to achieve hybridisation between nucleic acid molecules of a specified homology is:

$$T_m = 81.5^0 C + 16.6 \text{ Log } [Na^+] + 0.41[\ \% G + C] - 0.63\ (\%\text{formamide})$$

In a further preferred method of the invention the nucleic acid molecule is genomic DNA or cDNA.

In a preferred method of the invention the nucleic acid molecule encodes a ligand of human origin.

In a further preferred method of the invention said embryonic stem cells are of human origin.

In a yet further preferred method of the invention the cell transfected with the nucleic acid according to the invention is a mammalian cell. Preferably the cell is selected from the following group: a chinese hamster ovary cell; murine primary fibroblast cell; human primary fibroblast cell; transformed mouse fibroblast cell-line STO.

According to a further aspect of the invention there is provided a method for inhibiting the differentiation of embryonic stem cells or embryonal carcinoma cells comprising:

i) providing at least one polypeptide, or active fragment thereof, wherein said polypeptide is an inhibitor of the *Wnt* signalling pathway.

ii) forming a culture comprising the polypeptide identified in (i) above with an embryonic stem cell; and

iii) growing said culture under conditions suitable for the maintenance of embryonic stem cells in an undifferentiated state.

In a preferred method of the invention said inhibitor of Wnt signalling is selected from the group comprising the active binding fragments thereof of the following polypeptides: frizzled related polypeptides (FRP); Wnt Inhibitory Factors (WIF); Dickkopf; Cerebrus.

In a further preferred method of the invention said inhibitor of Wnt signalling is selected from the group comprising the active binding fragments thereof of the following polypeptides: SFRP1; SFRP4; FRZB; SFRP2; FZD1; FZD2; FZD9; FZD3; FZD5; FZD4; FZD6; FZD7; DVL2; DVL3; GSK3B; AXIN1; APC; TCF1; WIF-1; CER 1; DKK1-4; SARP 2; SARP 3.

According to a further aspect of the invention there is provided a method for inhibiting the differentiation of embryonic stem cells or embryonal carcinoma cells comprising:

i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule encoding a Wnt inhibitory polypeptide;

b) a nucleic acid molecule which hybridises to the nucleic acid in (a) and which encodes a polypeptide capable of inhibiting *Wnt* signalling; and

c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.

ii) contacting the cell of (i) above with a culture of embryonic stem cells; and

iii) growing said culture under conditions suitable for the maintenance of embryonic stem cells in an undifferentiated state.

In a preferred method of the invention said cells express at least one Wnt inhibitory polypeptide selected from the group comprising the active binding fragments thereof of the following polypeptides: frizzled related polypeptides (FRP); Wnt Inhibitory Factors (WIF); Dickkopf; Cerebrus. Preferably said cells express at least one Wnt inhibitory polypeptide selected from the group comprising the active binding fragments thereof of the following polypeptides: SFRP1; SFRP4; FRZB; SFRP2; FZD1; FZD2; FZD9; FZD3; FZD5; FZD4; FZD6; FZD7; DVL2; DVL3; GSK3B; AXIN1; APC; TCF1; WIF-1; CER-1; DKK1-4

In a further preferred method of the invention the nucleic acid molecule is encoded by a nucleic acid molecule which hybridises under stringent hybridisation conditions to the nucleic acid molecules represented in (a), (b) or (c) above. Preferably said inhibitors are human.

According to a further aspect of the invention there is provided a vector comprising the nucleic acid molecule according to the invention. Preferably the vector is an expression vector adapted for the expression of the polypeptide encoded by said nucleic acid molecule.

Typically said adaptation includes, by example and not by way of limitation, the provision of transcription control sequences (promoter sequences) which mediate cell/tissue specific expression. These promoter sequences may be cell/tissue specific, inducible or constitutive.

Promoter is an art recognised term and, for the sake of clarity, includes the following features which are provided by example only, and not by way of limitation. Enhancer elements are *cis* acting nucleic acid sequences often found 5' to the transcription initiation site of a gene (enhancers can also be found 3' to a gene sequence or even located in intronic sequences and is therefore position independent). Enhancers function to increase the rate of transcription of the gene to which the enhancer is linked. Enhancer activity is responsive to *trans* acting transcription factors (polypeptides) which have been shown to bind specifically to enhancer elements. The binding/activity of transcription factors (please see Eukaryotic Transcription Factors, by David S Latchman, Academic Press Ltd, San Diego) is responsive to a number of environmental cues which include, by example and not by way of limitation, intermediary metabolites (eg glucose, lipids), environmental effectors (eg light, heat,).

Promoter elements also include so called TATA box and RNA polymerase initiation selection (RIS) sequences which function to select a site of transcription initiation. These sequences also bind polypeptides which function, *inter alia*, to facilitate transcription initiation selection by RNA polymerase.

Adaptations also include the provision of selectable markers and autonomous replication sequences which both facilitate the maintenance of said vector in either the eukaryotic cell or prokaryotic host. Vectors which are maintained autonomously are referred to as episomal vectors. Episomal vectors are desirable since these molecules can incorporate large DNA fragments (30-50kb DNA). Episomal vectors of this type are described in WO98/07876. Alternatively, the vector is an integrating vector.

Adaptations which facilitate the expression of vector encoded genes include the provision of transcription termination/polyadenylation sequences. This also includes the provision of internal ribosome entry sites (IRES) which function to maximise expression of vector encoded genes arranged in bicistronic or multi-cistronic expression cassettes.

These adaptations are well known in the art. There is a significant amount of published literature with respect to expression vector construction and recombinant DNA techniques in general. Please see, Sambrook et al (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbour Laboratory, Cold Spring Harbour, NY and references therein; Marston, F (1987) DNA Cloning Techniques: A Practical Approach Vol III IRL Press, Oxford UK; DNA Cloning: F M Ausubel et al, Current Protocols in Molecular Biology, John Wiley & Sons, Inc.(1994).

Conventional methods to introduce DNA or vector DNA into cells are well known in the art and typically involve the use of chemical reagents, cationic lipids or physical methods. Chemical methods which facilitate the uptake of DNA by cells include the use of DEAE –Dextran (Vaheri and Pagano Science 175: p434) . DEAE-dextran is a negatively charged cation which associates and introduces the DNA into cells but which can result in loss of cell viability. Calcium phosphate is also a commonly used chemical agent which when co-precipitated with DNA introduces the DNA into cells (Graham et al Virology (1973) 52: p456).

The use of cationic lipids (eg liposomes, Felgner (1987) Proc.Natl.Acad.Sci USA, 84:p7413) has become a common method since it does not have the degree of toxicity shown by the above described chemical methods. The cationic head of the lipid associates with the negatively charged nucleic acid backbone of the DNA to be introduced. The lipid/DNA complex associates with the cell membrane and fuses with the cell to introduce the associated DNA into the cell. Liposome mediated DNA transfer has several advantages over existing methods. For example, cells which are

recalcitrant to traditional chemical methods are more easily transfected using liposome mediated transfer.

More recently still, physical methods to introduce DNA have become effective means to reproducibly transfect cells. Direct microinjection is one such method which can deliver DNA directly to the nucleus of a cell (Capecchi (1980) Cell, 22:p479). This allows the analysis of single cell transfectants. So called "biolistic" methods physically shoot DNA into cells and/or organelles using a particle gun (Neumann (1982) EMBO J, 1: p841). Electroporation is arguably the most popular method to transfect DNA. The method involves the use of a high voltage electrical charge to momentarily permeabilise cell membranes making them permeable to macromolecular complexes. However physical methods to introduce DNA do result in considerable loss of cell viability due to intracellular damage. These methods therefore require extensive optimisation and also require expensive equipment.

More recently still a method termed immunoporation has become a recognised techinque for the introduction of nucleic acid into cells, see Bildirici et al, Nature 405, 769. The technique involves the use of beads coated with an antibody to a specific receptor. The transfection mixture includes nucleic acid, typically vector DNA, antibody coated beads and cells expressing a specific cell surface receptor. The coated beads bind the cell surface receptor and when a shear force is applied to the cells the beads are stripped from the cell surface. During bead removal a transient hole is created through which nucleic acid and/or other biological molecules, eg polypeptides, can enter. Transfection efficiency of between 40-50% is achievable depending on the nucleic acid used.

Other non-liposome based, chemical transfectant agents have become available, for example ExGen500 (polyethylenimine), produced by MBI Fermentas. ExGen500 is particularly effective for transfection of human ES cells (Eiges, 2001).

According to a further aspect of the invention there is provided a method for the production of the polypeptide encoded by the nucleic acid molecule according to the invention comprising:

i) providing a cell transformed/transfected with a nucleic acid molecule according to the invention;

ii) growing said cell in conditions conducive to the manufacture of said polypeptide; and

i) purifying said polypeptide from said cell, or its growth environment.

In a preferred method of the invention said nucleic acid molecule is the vector according to the invention.

In a further preferred method of the invention said vector encodes, and thus said recombinant polypeptide is provided with, a secretion signal to facilitate purification of said polypeptide.

According to a further aspect of the invention there are provided host cells which have been transformed/transfected with the vector according to the invention, so as to include at least part of the polypeptide according to the invention, so as to permit expression of at least the functional part of the polypeptide encoded by said nucleic acid molecule.

Ideally said host cells are eukaryotic cells, for example, insect cells such as cells from a species *Spodoptera frugiperda* using the baculovirus expression system.

According to a further aspect of the invention there is provided a therapeutic cell composition comprising differentiated or differentiating embryonic stem cells derived by the method according to the invention. Preferably said composition is for

use in the treatment of: Parkinson's disease; Huntington's disease; motor neurone disease; heart disease; diabetes; liver disease (eg cirrhosis); renal disease; AIDS.

According to a further aspect of the invention there is provided a method of treatment of an animal comprising administering a cell composition comprising embryonic stem cells which have been induced to differentiate into at least one cell-type.

According to a yet further aspect of the invention there is provided condition medium obtained by culturing embryonic stem cells according to any of the methods hereindisclosed.

An embodiment of the invention will know be described by example only and with reference to the following figures:

Figure 1 is a schematic represenation of conserved domains in Notch polypeptides;

Figure 2 is the nucleic acid sequence of murine notch ligand delta-like 1;

Figure 3 is the amino acid sequence of murine notch ligand delta-like 1;

Figure 4 is the nucleic acid sequence of murine notch ligand jagged 1;

Figure 5 is the nucleic acid sequence of human notch ligand jagged 1 (alagille syndrome) (JAG1);

Figure 6 is the amino acid sequence of human notch ligand jagged 1 (alagille syndrome);

Figure 7 is the nucleic acid sequence of human notch ligand jagged 2 (JAG2)

Figure 8 is the amino acid sequence of human notch ligand jagged 2 (JAG2);

Figure 9 is the amino acid sequence of murine notch ligand jagged 1;

Figure 10 is the nucleic acid sequence of murine notch ligand jagged 2;

Figure 11 is the amino acid sequence of murine notch ligand jagged 2;

Figure 12 is the nucleic acid sequence of human notch ligand delta-like 3 (DLL3);

Figure 13 is the amino acid sequence of human notch ligand delta-like 3 precursor polypeptide;

Figure 14 is the nucleic acid sequence of human notch ligand delta-1 (DLL1);

Figure 15 is the amino acid sequence of murine notch ligand delta- like 1;

Figure 16 is the nucleic acid sequence of human notch ligand delta-like 4 (DLL4);

Figure 17 is the amino acid sequence of human notch ligand delta-like 4 (DLL4);

Figure 18 is the nucleic acid sequence of murine notch ligand delta-like 4(DLL4);

Figure 19 is the amino acid sequence of murine notch ligand delta-like 4(DLL4);

Figure 20 is a western blot of cell extracts of various EC cell-lines probed with Notch 2 antisera;

Figure 21 represents northern blot analysis of the expression patterns of notch genes (*Notch 1,2,3*) and notch ligands (*Dlk, jagged 1)* in EC cells and EC cells treated with retinoic acid (RA);

Figure 22 represents the nucleic acid sequence of human *Wnt 13*;

Figure 23 is a diagramatic representation of the Wnt signalling pathway;

Figure 24 represents northern blot analysis of *Wnt 13* and mRNA's corresponding to Frizzled receptors and Frizzled related protein antagonists of Wnt signalling in NTERA 2 cells various Wnt inhibitors after exposure of NTERA 2 cells;

Figure 25 represents a northern blot analysis of intracellular components of Wnt signalling pathway in NTERA 2 cells;

Figure 26 represents the nucleic acid sequence of human *dickkopf1*;

Figure 27 represents the nucleic acid sequence of human *dickkopf2*;

Figure 28 represents the nucleic acid sequence of human *dickkopf3*; and

Figure 29 represents the nucleic acid sequence of human *dickkopf4*;

Figure 30 represents the nucleic acid sequence of WNT-1;

Figure 31 represents the amino acid sequence of WNT-1;

Figure 32 represents the nucleic acid sequence of WNT-2;

Figure 33 represents the amino acid sequence of WNT-2;

Figure 34 represents the nucleic acid sequence of WNT 2B;

Figure 35 represents the amino acid sequence of WNT 2B;

Figure 36 represents the nucleic acid sequence of WNT 3;

Figure 37 represents the amino acid sequence of WNT 3;

Figure 38 represents the nucleic acid sequence of WNT 4;

Figure 39 represents the amino acid sequence of WNT 4;

Figure 40 represents the nucleic acid sequence of WNT 5A;

Figure 41 represents the amino acid sequence of WNT 5A;

Figure 42 represents the nucleic acid sequence of WNT 6;

Figure 43 represents the amino acid sequence of WNT 6;

Figure 44 represents the nucleic acid sequence of WNT 7A;

Figure 45 represents the amino acid sequence of WNT 7A;

Figure 46 represents the amino acid sequence of WNT 7B;

Figure 47 represents the nucleic acid sequence of WNT 8B;

Figure 48 represents the amino acid sequence of WNT 8B;

Figure 49 represents the nucleic acid sequence of WNT 10B;

Figure 50 represents the amino acid sequence of WNT 10B;

Figure 51 represents the nucleic acid sequence of WNT 11;

Figure 52 represents the amino acid sequence of WNT 11;

Figure 53 represents the nucleic acid sequence of WNT 14

Figure 54 represents the amino acid sequence of WNT 14;

Figure 55 represents the nucleic acid sequence of WNT 16;

Figure 56 represents the amino acid sequence of WNT 16;

Figure 57 represents the nucleic acid sequence of FZD 1;

Figure 58 represents the amino acid sequence of FZD 1;

Figure 59 represents the nucleic acid sequence of FZD 2;

Figure 60 represents the amino acid sequence of FZD 2;

Figure 61 represents the nucleic acid sequence of FZE 3;

Figure 62 represents the amino acid sequence of FZE 3;

Figure 63 represents the nucleic acid sequence of FZD 4;

Figure 64 represents the amino acid sequence of FZD 4;

Figure 65 represents the nucleic acid sequence of FZD 5;

Figure 66 represents the amino acid sequence of FZD 5;

Figure 67 represents the nucleic acid sequence of FZD 6;

Figure 68 represents the amino acid sequence of FZD 6;

Figure 69 represents the nucleic acid sequence of FZD 7;

Figure 70 represents the amino acid sequence of FZD 7;

Figure 71 represents the nucleic acid sequence of FZD 8;

Figure 72 represents the amino acid sequence of FZD 8;

Figure 73 represents the nucleic acid sequence of FZD 9;

Figure 74 represents the amino acid sequence of FZD 9;

Figure 75 represents the nucleic acid sequence of FZD 10;

Figure 76 represents the amino acid sequence of FZD 10;

Figure 77 represents the nucleic acid sequence of FRP;

Figure 78 represents the amino acid sequence of FRP;

Figure 79 represents the nucleic acid sequence of SARP 1;

Figure 80 represents the amino acid sequence of SARP 1;

Figure 81 represents the nucleic acid sequence of SARP 2;

Figure 82 represents the amino acid sequence of SARP 2;

Figure 83 represents the nucleic acid sequence of FRZB;

Figure 84 represents the amino acid sequence of FRZB;

Figure 85 represents the nucleic acid sequence of FRPHE;

Figure 86 represents the amino acid sequence of FRPHE;

Figure 87 represents the nucleic acid sequence of SARP 3;

Figure 88 represents the amino acid sequence of SARP 3;

Figure 89 represents the nucleic acid sequence of CER 1;

Figure 90 represents the amino acid sequence of CER 1;

Figure 91 represents the nucleic acid sequence of DKK1;

Figure 92 represents the amino acid sequence of DKK1;

Figure 93 represents the nucleic acid sequence of DKK 2;

Figure 94 represents the amino acid sequence of DKK 2;

Figure 95 represents the nucleic acid sequence of DKK 3;

Figure 96 represents the amino acid sequence of DKK 3;

Figure 97 represents the nucleic acid sequence of DKK 4;

Figure 98 represents the amino acid sequence of DKK 4;

Figure 99 represents the nucleic acid sequence of WIF-1;

Figure 100 represents the amino acid sequence of WIF-1;

Figure 101 represents the nucleic acid sequence of SRFP 1;

Figure 102 represents the amino acid sequence of SRFP 1;

Figure 103 represents the nucleic acid sequence of SRFP 4;

Figure 104 represents the amino acid sequence of SRFP 4; and

Figure 105 represents a diagram depicting the pCMV-tracer vector.

Materials and Methods

Table 1 Cell lines derived from germ cell tumours.

Cell Line	Biopsy Site	Biopsy Histology	Xenograph Histology	Reference
2102Ep	Testis	EC, T, Y	EC	(Andrews *et al.*, 1980)
833KE	Testis	EC, T, C, S	EC	(Andrews *et al.*, 1980)
TERA-1	Lung	EC, T		(Fogh and Trempe, 1975)
NTERA2 cl. D1	Lung	EC, T	EC, T	(Fogh and Trempe, 1975) (Andrews, 1984)

Abbreviations used: EC, embryonal carcinoma, T, teratoma, S, seminoma, C, choriocarcinoma, Y, yolk-sac carcinoma

Cell Lines derived from gestational choriocarcinomas.

BEWO	Corresponds to gestational choriocarcinoma	(Pattillo and Gay, 1968)

List of Antibodies Used

Antibody	Reference	References
SSEA-3	Andrews et. al., 1982	12
SSEA-4	Kannagi et. al., 1983	18
Tra-1-60	Andrews et. al., 1984	25
Tra-1-81	Andrews et. al., 1984	25
Tra-2-54	Andrews et. al., 1984	20
Tra-2-49	Andrews et. al., 1984	20
A2B5	Fenderson et. al., 1987	
ME311	Fenderson et. al., 1987	
Vin-is-56	Andrews et. al., 1990	44
Vin-is-53	Andrews et. al., 1990	44
Vin-2PB-22	Andrews et. al., 1990	44
Thy-1	Andrews et. al., 1983	10

Expression Vectors

The following mammlian expression vectors are used in the expression of ligands hereindisclosed:

Purchased from Stratagene Inc. pExchange-1; pExchange-2; pExchange-3A, 3B, 3C; pExchange-4A, 4B, 4C; pExchange-5A, 5b,5C; pExchange-6A, 6B, 6C; pExchange module EC-hyg; pExchange module EC-Puro; pExchange module EC-Neo; pCMV-Script; pCMV-Tag1; pCMV-Tag2; pCMV-Tag3; pCMV-Tag4; pCMV-Tag5; pCMVLACI, pOPRSVI/MCS, pOPI3-CAT ; pERV3; pEGSH.

Purchased from Invitrogen Inv.

T-REX System vectors

pcDNA4/TO; pcDNA4/TO/myc-His; pcDNA6/TR; pT-Rex-DEST30; pT-Rex-DEST31; pcDNA4/TO-E; pcDNA5/FRT/TO; pcDNA5/FRT/TO-TOPO.

Geneswitch System vectors

pGene/V5-His A, B, C; pSwitch

Ecdysone-Inducible System

PVgRXR; pIND; pIND(SP1); pIND/V5-His; pIND/V5-His-TOPO; pIND/GFP; pIND(SP1)/GFP.

PShooter vectors

pRF/Myc/Nuc; pCMV/Myc/nuc; pEF/myc/mito; pCMV/myc/mito; pEF/myc/ER; pCMV/myc/ER; pEF/myc/cyto; pCMV/myc/cyto.

INVITROGEN INC

pTet-off; pTet-on; ptTA-2/ /3 /4; pTet-tTS; pTRE2hyg
PTRE2pur; pTRE2; pLP-TRE2; PTRE-Myc; pTRE-HA; pTRE-6xHN
pTRE-d2EGFP; pBI; pBI-EGFP; pBI-G; pBI-L;pTK-Hyg

"Living colours" vectors.

pDsRed2-N1; pDsRed2-C1; pECFP-N1; pEGFP-N1; pEGFP-N2; pEGFP-N3
pEYFP-N1; pECFP-C1; pEGFP-C1; pEGFP-C2; pEGFP-C3
pEYFP-C1; pd1EGFP-N1; pd1ECFP-N1; pd2EGFP-N1; pd2EYFP-N1
pd4EGFP-N1; pCMS-EGFP; pHygEGFP; pEGFPLuc; pNF-κB-dsEGFP
pIRES2-EGFP; pIRES-EYFP

Maintenance of cell lines

All cells were grown in Dulbecco's modified Eagle's medium (DMEM), supplemented with 10% by volume foetal calf serum (Gibco BRL) and 2mM L-glutamine. Tissue culture flasks were incubated in a humidified atmosphere of 10% CO_2 in air at 37°C.

Treatment of NTERA2 Cells

Retinoic acid

Medium was aspirated from confluent flasks of EC cells and the cells rinsed in sterile PBS. 1ml of 0.25% (w/v) trypsin in 2mM EDTA was added per $75cm^2$ flask and the flask incubated at room temperature for up to 5 minutes. Vigorous shaking was subsequently used to dislodge the cells. Cells were suspended in 9ml of supplemented DMEM per ml of trypsin used and counted in a haemocytometer. Cells were seeded at 10^6 cells per $75cm^2$ flask, in medium containing 10^{-5}M all-*trans*-retinoic acid (Eastman Kodak), diluted from a 10^{-2}M stock solution in dimethyl sulfoxide (DMSO). Flasks were incubated as described above and the media replaced as and when required.

Hexamethylene bisacetamide (HMBA)

Cells to be treated with HMBA were prepared as described for retinoic acid, but grown in medium supplemented with 10^{-3}M HMBA instead of RA.

Harvesting of cells

Cells were dislodged from the culture vessel with trypsin and suspended in 9ml culture medium per ml of trypsin solution used, as described above. The cell suspension was then centrifuged at 400 x g for 3 minutes and the medium aspirated from the resulting cell pellet. Cells were then rinsed in 5ml PBS and centrifuged again at 400 x g for 1 minute. The PBS rinse was aspirated and the cells stored at –80°C or used immediately.

Total RNA preparation

Where possible, all vessels and all solutions used in RNA preparation and storage were treated with a 0.01% (v/v) solution of diethylpyrocarbonate (DEPC) in distilled water, and subsequently autoclaved.

TRI reagent (Sigma) was added to pelleted cells in a quantity corresponding to 1ml per 75cm^2 flask. The lysate was agitated until homogenous. 0.2ml of chloroform was added per ml of TRI reagent used and the vessel vortexed for 10 seconds. After 10 minutes at room temperature, the lysate was centrifuged at 12000 x g for 15 minutes at 4°C. Following centrifugation, the aqueous (uppermost) phase was transferred to a fresh vessel and 0.5ml of isopropanol added per ml of TRI reagent used. The sample was incubated at room temperature for 10 minutes, then centrifuged at 12000 x g for 10 minutes at 4°C. Following centrifugation, the supernatant was removed and the pellet washed in 70% ethanol. RNA was dissolved in DEPC-treated, double-distilled water.

Isolation of mRNA

100mg oligo dT cellulose (Ambion) was suspended in 25ml binding buffer. Up to 2mg of total RNA was then added to the binding buffer and the suspension gently agitated at room temperature for 45 minutes. The suspension was then centrifuged at 3000 x g for 10 minutes and the supernatant discarded. The resulting pellet was re-suspended in a further 25ml of binding buffer and agitated at room temperature for 60 minutes. The suspension was again centrifuged at 3000 x g and the supernatant discarded. The pellet of oligo dT cellulose was transferred to a spin column using a minimal quantity of binding buffer to re-suspend. The column was spun at maximum speed in a desktop microfuge for 30 seconds and the eluate discarded. This was repeated until the cellulose was dry. 200µl of wash buffer was then added to the cellulose and mixed in with a pipette tip. The column was spun at maximum speed for 1 minute and the eluate discarded. 200µl of DEPC-treated, double-distilled H_2O was then added to the cellulose and mixed in, as before. The column was then spun at maximum speed for 2 minutes and the eluted mRNA collected.

Precipitation of RNA

To the RNA solution was added 0.1x volume of 5M LiCl and 2.5x volume of 100% ethanol. After vortexing briefly, the sample was incubated at –20°C for >60 minutes

to precipitate. Precipitated RNA was centrifuged at maximum speed in a bench top microfuge for 30 minutes. The supernatant was discarded and the pellet rinsed in 70% ethanol, then dissolved in H_2O.

Quantitation of nucleic acid

A Beckman DU 650 spectrophotometer was used for the quantitation of both DNA and RNA. The machine was set to measure absorbence at wavelengths of 260nm and 280nm. After blanking the machine on an appropriate solution, diluted DNA or RNA samples in a volume of 100µl were added to the cuvette and measured. The absorbence at 260nm was used to calculate nucleic acid concentration in µg/µl, as shown below:

$$[\text{Nucleic acid}] = (A^{260} \times N \times DF) \div 1000$$

Where N is 33 for single-stranded DNA, 50 for double-stranded DNA and 40 for RNA and DF is the dilution factor for the sample added to the cuvette.

Northern blot analysis

Blot preparation

1g of agarose was dissolved in 85ml H_2O by boiling. After cooling to around 70°C, 10ml of 10x MOPS buffer and 5ml of formaldehyde were added, and the gel cast. 1-5µg of each mRNA sample was mixed with an appropriate quantity of 10x RNA loading buffer to give a final volume of no more than 30µl. The RNA was then denatured at 95°C for 2 minutes and quenched on ice for 10 minutes. The gel was placed in an electrophoresis tank containing 1x MOPS buffer and the samples loaded into each well of the gel, along with appropriate molecular weight markers in the outermost wells. 80V were applied across the gel for 2-3 hours or as required. Following electrophoresis, the outermost lanes containing the molecular weight markers were removed using a scalpel and submerged in double-distilled H_2O containing ethidium bromide at 0.5µg/ml. The remainder of the gel was submerged in >5 volumes of double-distilled H_2O, which was replaced every 5 minutes for a total

of 25 minutes. An appropriately sized piece of GeneScreen Plus (DuPont) membrane, just larger than the area of gel to be blotted, was cut. The membrane was hydrated by briefly submerging in double-distilled H_2O, then transferred to 10x SSC, concurrent with the last 15 minutes of gel washing. The blotting apparatus was assembled as shown in Figure 2.1, with the gel upside-down, using 10x SSC transfer buffer. After transfer of at least 6 hours, the absorbent material was removed from the membrane. After marking the position of the wells using a pencil, the membrane was removed from the gel and washed briefly in 2x SSC. Whilst still damp, the RNA was fixed to the membrane by UV crosslinking. The membrane was then baked at 80°C for 3 hours.

The excised marker lanes were de-stained by soaking in a large volume of double-distilled H_2O for around 3 hours, after which they were visualised on a UV transilluminator and photographed.

Probe preparation

Random-primed DNA labelling was carried out using the Prime-a-Gene kit from Promega. Approximately 25ng of template DNA (PCR or restriction digest product) was denatured at 95°C for 2 minutes, then quenched on ice for 10 minutes. The reaction mix was then assembled on ice, in the order indicated below:

10µl of 5x labelling buffer
H_2O to give a final volume of 50µl
2µl unlabelled dNTP mix (0.5mM each)
25ng of denatured/quenched template DNA
2µl 10mg/ml BSA
5µl αP^{32}dATP 3000Ci/mmol (NEN DuPont)
1µl DNA polymerase 1 large (Klenow) fragment

The labelling reaction mix was incubated at room temperature for 2 hours. After this period, unincorporated nucleotides were removed using Pharmacia S-300 MicroSpin columns. Columns were placed in a microfuge tube and pre-spun at 735 x g for 1 minute. The column was then transferred to a fresh tube and the entire labelling reaction added. The column was then spun at 735 x g for a further 2 minutes and the purified, labelled DNA collected. Labelled DNA was denatured at 95°C for 2 minutes, then quenched on ice for 15 minutes.

Hybridisation and washing procedure

Northern blots were equilibrated in 150ml of 2x SSC at 42°C for 15 minutes in a hybridisation oven at 8 RPM. The SSC was exchanged for 25ml of hybridisation buffer, pre-warmed to 42°C, and the filter incubated for a further 30 minutes at the same temperature. The entire volume of purified probe solution was then added to the hybridisation buffer and the blot incubated overnight at 42°C/ 8 RPM. The hybridisation solution was then discarded and the blot washed as follows:

2x SSC at room temperature for 20 minutes
2x SSC at room temperature for 20 minutes
2x SSC/1% SDS at 65°C for 45 minutes
2x SSC/1% SDS at 65°C for 45 minutes
0.1x SSC at room temperature for 20 minutes
0.1x SSC at room temperature for 20 minutes

Filters were exposed to a Bio Rad BI phosphor-imager screen overnight and, in most cases, subsequently exposed to X-ray film (Kodak X-omat AR).

Loading controls for Northern blots

All Northern blots used in this study were probed with β-actin as a loading control. Table 2.5 (overleaf) lists the figures to which each control probing (panel A to T, Figure 2.2) corresponds. Northern blot data presented in this study have not, in all

cases, been subject to repeat experiments using RNA isolated from different batches of cells. These data may not be regarded as conclusive, since reproducibility has not been proven.

Method for Analysis of the Requirement for Notch Ligands in the Differentiation of Embryonic Stem, Embryonal Carcinoma and their Differentiated Derivatives.

CHO are transfected with constructs encoding either membrane bound or soluble forms of the Notch ligands. These cell lines are used to support the growth of either Embryonal carcinoma cells (EC) e.g NTERA2/cl.D1 or Human embryonic stem cells (hES).

The transfected CHO cells (CHO(DSL)) are used in the following way. To assess membrane bound forms of the Notch ligands the CHO(DSL) cells are used as feeder cells (i.e. the EC or hES will be grown on top of the CHO(DSL) cells). To assess the soluble forms of the Notch ligands either supernatant from the transfected CHO cells or concentrated ligand molecules derived from the supernatant are added to the culture medium of the EC and hES cells.

Notch Ligand Constructs.

The following cloned Notch ligands were obtained from Dr. Shigeru Chiba, Department of Hematology, Oncology and Cell Therapy, Transplantation Medicine. Graduate School of Medicine. University of Tokyo.

Delta1-FLAG
Jagged1-FLAG
Jagged2-FLAG

Soluble Delta1-Fc
Soluble Jagged1-Fc

Soluble Jagged2-Fc

These had been cloned into the vector pTRACER-CMV from Invitrogen, Fig 30).

The clones used consisted either of the full length ligand linked to a histidine tag (FLAG, Kodak Inc.), or a ligand lacking the membrane spanning and intracellular portion of the protein thus rendering the ligand soluble. These had been linked to the Fc portion of human IgG.

Generation of Notch Ligand expressing Cell lines

The Chinese Hamster Ovary derived cell line AA8 was maintained in MEM Alpha medium with Glutamax-1 supplemented with ribonucleosides and deoxyribonucleosides (Lifetechnologies) and 10% Foetal Bovine Serum (FBS)(Lifetechnologies).

Plasmid was transfected into the AA8 cells using either Fugene (Roche) or Lipofectin (Lifetechnologies) or Superfect (Qiagen) according to manufacturers protocols.

Assessment of Transiently Transfected Cell lines for Ligand Production.

Both soluble and membrane bound forms of the Notch ligand's production are assayed by western blotting and chemiluminesent detection.

Cells transfected with the ligand encoding constructs are harvested and the proteins extracted. Due to the tagging of the ligands proteins are able to be run out on an SDS-PAGE gel, blotted and probed with either mouse anti-FLAG antibody and detected using a anti-mouse HRP secondary or an HRP-secondary antibody. Both methods use electro-chemiluminecence (ECL) as the detection method.

Concentration of Soluble Notch ligand from the Supernatant of Transfected CHO cells.

Fc-labelled Notch ligand can be purified from transfected CHO cells supernatant using a HiTrap protein G HP column (Amersham Pharmacia Biotech). A sample can be analysed by western blotting as described above.

Embryonic Cell culture.

Human Embryonal Carcinoma NTERA2/D1 cells are maintained in Dulbecco's modified Eagles medium (DMEM), supplemented with 2mM l-glutamine, 10% Foetal Bovine Serum (Lifetechnologies) and at 37°C under 10% CO_2 in air. Cells were passaged by scraping from the surface of the tissue culture flask with 3mm glass beads and reseeded at 5 x 10^6 cells per 75cm^3 flask. For specific seeding densities cells were pasaaged using 0.25% Trypsin (Lifetechnologies) in Dulbecco's Phosphate Buffered Saline (PBS) supplemented with 1mM EDTA.

Human Embryonic Stem Cells are maintained on irradiated mouse embryonic fibroblasts in serum free conditions, with 80% F12:DMEM (Lifetechnologies), 20% Knockout SR (Lifetechnologies), 1% Non-essential amino acid solution (Lifetechnologies), 1 mM L-glutamine, 0.1mM β-mercaptoetanol (Sigma) 4 ng/ml bFGF (Sigma). The cells are passaged using collagenase IV and scraping.

Flow Cytofluorimetry

Cells were removed from their adherent culture surface and incubated with suitable primary antibody for 1 hour at 4C. Cells are washed in PBS with 5% FCS and incubated for a further hour with a suitable FITC-conjugated labelled secondary antibody, and analysed on a EPICS Elite ESP Flow Cytometer (Coulter Electronics). Colonies were assessed for the presence of embryonal stem cell markers such as SSEA-3, -4, Tra-1-60 and for appearance of markers of differentiated marker antigens such as A2B5, ME311 and N901.

Design of oligonucleotide primers

Primers for use in PCR were designed on a Macintosh Power PC, using the "Primer Select" program of the DNASTAR software package (DNASTAR Inc.). All primers used in this study are shown in Table 2

Table 2 List of oligonucleotide primers

Gene	GenBank accession	Primer direction	Prinmer location	Primer sequence 5' to 3'
Wnt-13	Z71621	Forward	1159-1178	Tgagtggttcctgtactctg
		Reverse	1503-1484	Actcacactgggtaacacgg
SFRP4	XM_004706	Forward	858-880	Agaggagtggctgcaatgaggtc
		Reverse	1159-1142	Gcgcccggctgttttctt
Waf1	U03106	Forward	487-506	Cagggtcgaaaacggcggca
		Reverse	947-928	Aggagccacacccctccaga
β-actin	NM_001101	Forward	326-357	Atctggcaccacaccttctacaatgagctgcg
		Reverse	1163-1132	Cgtcatactcctgcttgctgatccacatctgc
neuroD1	NM_002500	Forward	240-263	Aagccatgaacgcagaggaggact
		Reverse	818-799	Agctgtccatggtaccgtaa

All PCR data presented in this study were duplicated in independent experiments to eliminate the possibility of methodological error. However, duplicate experiments were performed on identical samples and do not, therefore, control for variability between separate batches of cells. Polymerase chain reactions from which quantitative interpretations were to be made were controlled by parallel amplification of the cyclin-dependent kinase inhibitor, *Waf*1. This transcript has been demonstrated by other workers in the laboratory to be constitutively expressed by NTERA2 EC cells and differentiated derivatives (unpublished data). Furthermore, *Waf*1 has been shown to exhibit an approximately 20-fold lower abundance in the NTERA2 system than the more widely used control, β-actin, and is therefore well suited to the analysis of rare transcripts.

PCR Reaction conditions

PCR mixes were assembled on ice, with the following components per reaction:

5μl of 25mM $MgCl_2$
5μl of 10x reaction buffer
5μl of 1mM dNTPs
3μl of forward primer at 5pmol/μl
3μl of reverse primer at 5pmol/μl
0.3μl of Taq polymerase at 1 unit/μl (Promega)
template and H_20 to give 50μl final volume

A premix was made containing all reaction components bar the template. Premix was then added to the reaction vessels containing the template, on ice. The reaction vessels were then transferred to the thermal cycler. The PCR programs used are shown in Table 3, with cycling from T1➾T2➾T3➾T1.

Table 3 PCR thermal cycling programs

	Program 1	Program 2	Program 3	Program 4
T1 (temp/duration)	96°C/30 seconds	94°C/60 seconds	94°C/90 seconds	95°C/90 seconds
T2 (temp/duration)	50°C/15 seconds	55°C/90 seconds	60°C/90 seconds	63°C/60 seconds
T3 (temp/duration)	60°C/240 seconds	72°C/60 seconds	72°C/120 seconds	72°C/60 seconds
Cycles	25	35	35	35

List of DNA and protein accession numbers of genes used in results

Gene Name	Description	cDNA Accession Number	Protein Accession Number
WNT2B	wingless-type MMTV integration site family, member 2B	AB045116	Q93097

	member 2B		
SFRP1	secreted frizzled-related protein 1	AF056087	AAC12877
SFRP4	secreted frizzled-related protein 4	AF026692	AAC04617
FRZB	frizzled-related protein	NM_001463	NP_001454
SFRP2	secreted frizzled-related protein 2		
FZD1	frizzled (Drosophila) homolog 1	AB017363	BAA34666
FZD2	frizzled (Drosophila) homolog 2	NM_001466	NP_001457
FZD9	frizzled (Drosophila) homolog 9	HSU82169	AAC51174
FZD3	frizzled (Drosophila) homolog 3	Kirikoshi et. al., 2000	Kirikoshi et. al., 2000
FZD5	frizzled (Drosophila) homolog 5		
FZD4	frizzled (Drosophila) homolog 4	NM_012193	NP_036325
FZD6	frizzled (Drosophila) homolog 6	AB012911	BAA25686
FZD7	frizzled (Drosophila) homolog 7	AB017365	BAA34668
DVL2	dishevelled 2 (homologous to Drosophila dsh)	NM_004422	NP_004413
DVL3	dishevelled 3 (homologous to Drosophila dsh)	NM_004423	NP_004414
GSK3B	glycogen synthase kinase 3 beta	NM_002093	NP_002084
AXIN1	axin	AF009674	AAC51624
APC	adenomatosis polyposis coli	NM_000038	NP_000029
TCF1	transcription factor 1, hepatic; LF-B1, hepatic nuclear factor (HNF1), albumin proximal factor	M57732	AAA88077

__Examples__

Expression of a single Wnt gene, Wnt-13(2B) was detected. This transcript was absent in NTERA2 EC cells, but showed marked up-regulation following RA treatment, figure 24. Members of the FRP family, encoding putative Wnt antagonists,

also showed altered expression during differentiation, figure 24. Both Frp-1 and SARP-1 were down-regulated following RA treatment, whilst FrpHE was absent in EC cells, but expressed at high levels in RA treated cultures.

Several members of the frizzled family were also detected, providing a candidate receptor system for Wnt-13, figure 24. Two of these, hFz-4 and hFz-6, showed developmental regulation. Transcripts corresponding to intracellular components of the Wnt pathway, including Dishevelled, GSK-3b, Axin, APC and TCF were present at equivalent levels in EC and differentiating cultures. CBP was also ubiquitously expressed.

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CLAIMS

1. A method to modulate the differentiation of an embryonic stem cell comprising:

i) providing a culture of embryonic stem cells;

ii) providing at least one ligand, or the active binding fragment thereof, capable of binding its cognate receptor polypeptide expressed by said embryonic stem cell;

iii) forming a culture comprising embryonic stem cells and said ligand; and

iv) growing said cell culture.

2. A method according to Claim 1 wherein said ligand is encoded by a nucleic acid molecule selected from the group consisting of:

i) a nucleic acid molecule as represented in Figure 22;

ii) a nucleic acid molecule which hybridises to the nucleic acid in (i) and which encodes a ligand capable of binding a Wnt receptor; and

iii) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (i) and (ii) above.

3. A method according to Claim 2 wherein said ligand is encoded by a nucleic acid molecule selected from the nucleic acid sequences represented in: Fig 30; Fig 32; Fig 34; Fig 36; Fig 38; Fig 40; Fig 42; Fig 44; Fig 47; Fig 49; Fig 51; Fig 53; Fig 55.

4. A method according to Claim 2 or 3 wherein said ligand is encoded by a nucleic acid molecule as represented by the nucleic acid sequence in Fig 22.

5. A method according to Claim 1 wherein said ligand is encoded by a nucleic acid molecule selected from the group consisting of:

i) a nucleic acid molecule as represented in Figures 2, 4, 5, 7, 10, 12, 14, 16, or 18.

ii) a nucleic acid molecule which hybridises to the nucleic acid in (i) and which encodes a ligand capable of modulating embryonic stem cell differentiation; and

iii) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (i) and (ii) above.

6. A method according to Claim 5 wherein said ligand is selected from the group comprising the amino acid sequences in Figures 3, 6, 8, 9, 11, 13, 15, 17, 19, or polypeptide variants thereof.

7. A method according to any of Claims 1-6 wherein said cells are induced to differentiate by the addition of at least one agent selected from the group consisting of: retinoic acid; hexamethylene bisacetamide; bone morphogenetic proteins; bromodeoxyuridine; lithium; sonic hedgehog.

8. A method for modulating the differentiation of embryonic stem cells comprising:

i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule as represented in Figures 2, 4, 5, 7, 10, 12, 14, 16, 18.

b) a nucleic acid molecule which hybridises to the nucleic acid in (ii) and which encodes a ligand capable of modulating embryonic stem cell differentiation; and

c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.

ii) forming a culture comprising the cell identified in (i) above with an embryonic stem cell; and

iii) growing said culture under conditions suitable for the maintenance and/or differentiation of said embryonic stem cell.

9. A method for modulating the differentiation of embryonic stem cells comprising:

i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:
   a) a nucleic acid molecule as represented by the sequence in Figure 22;
   b) a nucleic acid molecule which hybridises to the nucleic acid in (a) and which encodes a ligand capable of binding a Wnt receptor; and
   c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.

ii) forming a culture comprising a cell identified in (i) above with an embryonic stem cell; and

iii) growing said culture under conditions suitable for the maintenance and/or differentiation of embryonic stem cells.

10. A method according to Claim 9 wherein said cell expresses Wnt-13 ligand.

11. A method according to any of Claims 9 or 10 wherein said cells are induced to differentiate by the addition of at least one agent selected from the group consisting of: retinoic acid; hexamethylene bisacetamide; bone morphogenetic proteins; bromodeoxyuridine; lithium; sonic hedgehog.

12. A method according to any of Claims 1-11 wherein said nucleic acid molecule encodes a ligand of human origin.

13. A method according to any of Claims 1-12 wherein said embryonic stem cells are of human origin.

14. A method according to any of Claims 8-13 wherein said transfected cell is a

mammalian cell.

15. A cell according to Claim 14 wherein said cell is selected from the group consisting of: a chinese hamster ovary cell; murine primary fibroblast cell; human primary fibroblast cell; transformed mouse fibroblast cell-line STO.

16. A method for inhibiting the differentiation of embryonic stem cells comprising the steps of:

i) providing at least one polypeptide, or active fragment thereof, wherein said polypeptide is an inhibitor of the *Wnt* signalling pathway.

iii) forming a culture comprising the polypeptide identified in (i) above with an embryonic stem cell; and

iii) growing said culture under conditions suitable for the maintenance of embryonic stem cells in an undifferentiated state.

17. A method according to Claim 16 wherein said inhibitor is selected from the group consisting of the active binding fragments thereof of the following polypeptides: frizzled related polypeptides (FRP); Wnt Inhibitory Factors (WIF); Dickkopf; Cerebrus.

18. A method according to Claim 17 wherein said inhibitor is encoded by a nucleic acid molecule selected from the nucleic acid sequences represented by: Fig 57; Fig 59; Fig 61; Fig 63; Fig 65; Fig 67; Fig 69; Fig 71; Fig 73; Fig 75; Fig 77; Fig 79; Fig 81; Fig 83; Fig 85; Fig 87; Fig 89; Fig 91; Fig 93; Fig 95; Fig 97; Fig 99; Fig 101; or Fig 103.

19. A method for inhibiting the differentiation of embryonic stem cells comprising the steps of:

i) providing a cell transfected with a nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule encoding a Wnt inhibitory polypeptide;

b) a nucleic acid molecule which hybridises to the nucleic acid in (a) and which encodes a polypeptide capable of inhibiting *Wnt* signalling; and

c) nucleic acid molecules which are degenerate as a result of the genetic code to the sequences defined in (a) and (b) above.

ii) forming a culture of the cell identified in (i) above with an embryonic stem cell; and

iii) growing said culture under conditions suitable for the maintenance of embryonic stem cells in an undifferentiated state.

20. A method according to Claim 19 wherein said cells express at least one Wnt inhibitory polypeptide selected from the group consisting of the active binding fragments thereof of the following polypeptides: frizzled related polypeptides (FRP); Wnt Inhibitory Factors (WIF); Dickkopf; Cerebrus.

21. A method according to Claim 19 wherein said cells express at least one Wnt inhibitory polypeptide encoded by a nucleic acid molecule selected from the nucleic acid sequences represented by : Fig 57; Fig 59; Fig 61; Fig 63; Fig 65; Fig 67; Fig 69; Fig 71; Fig 73; Fig 75; Fig 77; Fig 79; Fig 81; Fig 83; Fig 85; Fig 87; Fig 89; Fig 91; Fig 93; Fig 95; Fig 97; Fig 99; Fig 101; Fig or 103.

22. A cell or cell culture obtainable by the method according to any of Claims 1-21.

23. A therapeutic cell composition obtainable by the method according to any of Claims 1-15.

24. Use of a cell according to Claim 23 for the manufacture of a composition for use in the treatment of a disease selected from the group consisting of: Parkinson's disease; Huntington's disease; motor neurone disease; heart disease; diabetes; liver disease (eg cirrhosis); renal disease; AIDS.

25. A method of treatment of an animal, preferably a human, comprising administering a cell composition comprising embryonic stem cells which have been induced to differentiate into at least one cell-type by the method according to any of Claims 1-14.

26. Condition medium obtained by culturing embryonic stem cells according to the method of any of Claims 1-21.

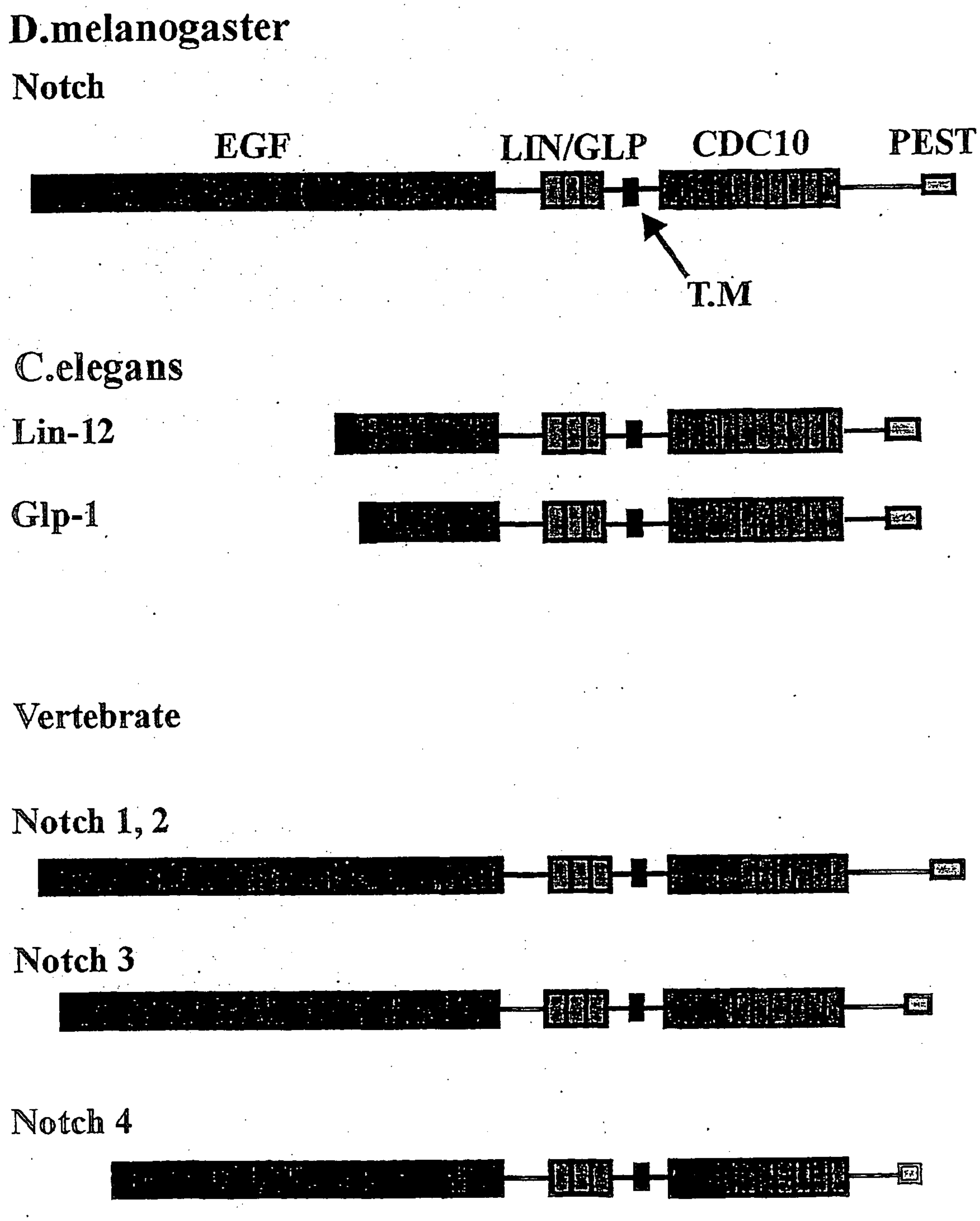
D.melanogaster
Notch
EGF
LIN/GLP
CDC10
PEST
T.M
C.elegans
Lin-12
Glp-1
Vertebrate
Notch 1, 2
Notch 3
Notch 4

Figure 1

Figure 2

GTCCAGCGGTACCATGGGCCGTCGGAGCGCGCTAGCCCTTGCCGTGGTCTCTGCCCTGC
TGTGCCAGGTCTGGAGCTCCGGCGTATTTGAGCTGAAGCTGCAGGAGTTCGTCAACAA
GAAGGGGCTGCTGGGGAACCGCAACTGCTGCCGCGGGGGCTCTGGCCCGCCTTGCGCC
TGCAGGACCTTCTTTCGCGTATGCCTCAAGCACTACCAGGCCAGCGTGTCACCGGAGCC
ACCCTGCACCTACGGCAGTGCTGTCACGCCAGTGCTGGGTGTCGACTCCTTCAGCCTGC
CTGATGGCGCAGGCATCGACCCCGCCTTCAGCAACCCCATCCGATTCCCCTTCGGCTTC
ACCTGGCCAGGTACCTTCTCTCTGATCATTGAAGCCCTCCATACAGACTCTCCCGATGA
CCTCGCAACAGAAAACCCAGAAAGACTCATCAGCCGCCTGACCACACAGAGGCACCTC
ACTGTGGGAGAAGAATGGTCTCAGGACCTTCACAGTAGCGGCCGCACAGACCTCCGGT
ACTCTTACCGGTTTGTGTGTGACGAGCACTACTACGGAGAAGGTTGCTCTGTGTTCTGC
CGACCTCGGGATGACGCCTTTGGCCACTTCACCTGCGGGGACAGAGGGGAGAAGATGT
GCGACCCTGGCTGGAAAGGCCAGTACTGCACTGACCCAATCTGTCTGCCAGGGTGTGA
TGACCAACATGGATACTGTGACAAACCAGGGGAGTGCAAGTGCAGAGTTGGCTGGCAG
GGCCGCTACTGCGATGAGTGCATCCGATACCCAGGTTGTCTCCATGGCACCTGCCAGC
AACCCTGGCAGTGTAACTGCCAGGAAGGCTGGGGGGGCCTTTTCTGCAACCAAGACCT
GAACTACTGTACTCACCATAAGCCGTGCAGGAATGGAGCCACCTGCACCAACACGGGC
CAGGGGAGCTACACATGTTCCTGCCGACCTGGGTATACAGGTGCCAACTGTGAGCTGG
AAGTAGATGAGTGTGCTCCTAGCCCCTGCAAGAACGGAGCGAGCTGCACGGACCTTGA
GGACAGCTTCTCTTGCACCTGCCCTCCCGGCTTCTATGGCAAGGTCTGTGAGCTGAGCG
CCATGACCTGTGCAGATGGCCCTTGCTTCAATGGAGGACGATGTTCAGATAACCCTGAC
GGAGGCTACACCTGCCATTGCCCCTTGGGCTTCTCTGGCTTCAACTGTGAGAAGAAGAT
GGATCTCTGCGGCTCTTCCCCTTGTTCTAACGGTGCCAAGTGTGTGGACCTCGGCAACT
CTTACCTGTGCCGGTGCCAGGCTGGCTTCTCCGGGAGGTACTGCGAGGACAATGTGGA
TGACTGTGCCTCCTCCCCGTGTGCAAATGGGGGCACCTGCCGGGACAGTGTGAACGAC
TTCTCCTGTACCTGCCCACCTGGCTACACGGGCAAGAACTGCAGCGCCCCTGTCAGCAG
GTGTGAGCATGCACCCTGCCATAATGGGGCCACCTGCCACCAGAGGGGCCAGCGCTAC
ATGTGTGAGTGCGCCCAGGGCTATGGCGGCCCCAACTGCCAGTTTCTGCTCCCTGAGCC
ACCACCAGGGCCCATGGTGGTGGACCTCAGTGAGAGGCATATGGAGAGCCAGGGCGG
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GCTGTGCTGCTGTGGTGGTCTGCGTCCGGCTGAAGCTACAGAAACACCAGCCTCCACCT
GAACCCTGTGGGGGAGAGACAGAAACCATGAACAACCTAGCCAATTGCCAGCGCGAG
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CGGACTTTCACGGGGACCATGGAGCCAAGAAGAGCAGCTTTAAGGTCCGATACCCCAC
TGTGGACTATAACCTCGTTCGAGACCTCAAGGGAGATGAAGCCACGGTCAGGGATACA
CACAGCAAACGTGACACCAAGTGCCAGTCACAGAGCTCTGCAGGAGAAGAGAAGATC
GCCCCAACACTTAGGGGTGGGGAGATTCCTGACAGAAAAAGGCCAGAGTCTGTCTACT
CTACTTCAAAGGACACCAAGTACCAGTCGGTGTATGTTCTGTCTGCAGAAAAGGATGA
GTGTGTTATAGCGACTGAGGTGTAAGATGGAAGCGATGTGGCAAAATTCCCATTTCTCT
CAAATAAAATTCCAAGGATATAGCCCCGATGAATGCTGCTGAGAGAGGAAGGGAGAG
GAAACCCAGGGACTGCTGCTGAGAACCAGGTTCAGGCGAAGCTGGTTCTCTCAGAGTT
AGCAGAGGCGCCCGACACTGCCAGCCTAGGCTTTGGCTGCCGCTGGACTGCCTGCTGG
TTGTTCCCATTGCACTATGGACAGTTGCTTTGAAGAGTATATATTTAAATGGACGAGTG
ACTTGATTCATATAGGAAGCACGCACTGCCCACACGTCTATCTTGGATTACTATGAGCC
AGTCTTTCCTTGAACTAGAAACACAACTGCCTTTATTGTCCTTTTTGATACTGAGATGTG
TTTTTTTTTTTCCTAGACGGAAAAAGAAAACGTGTGTTATTTTTTTGGGATTTGTAAAA
ATATTTTTCATGATATCTGTAAAGCTTGAGTATTTTGTGACGTTCATTTTTTTATAATTT
AAATTTTGGTAAATATGTACAAAGGCACTTCGGGTCTATGTGACTATATTTTTTTGTAT
ATAAATGTATTTATGGAATATTGTGCAAATGTTATTTGAGTTTTTACTGTTTTGTTAAT

Figure 3

MGRRSALALAVVSALLCQVWSSGVFELKLQEFVNKKGLLGNRNCCRGGSGPPCACRTFFR
VCLKHYQASVSPEPPCTYGSAVTPVLGVDSFSLPDGAGIDPAFSNPIRFPFGFT,WPGTFSLIIE
ALHTDSPDDLATENPERLISRLTTQRHLTVGEEWSQDLHSSGRTDLRYSYRFVCDEHYYGE
GCSVFCRPRDDAFGHFTCGDRGEKMCDPGWKGQYCTDPICLPGCDDQHGYCDKPGECKC
RVGWQGRYCDECIRYPGCLHGTCQQPWQCNCQEGWGGLFCNQDLNYCTHHKPCRNGAT
CTNTGQGSYTCSCRPGYTGANCELEVDECAPSPCKNGASCTDLEDSFSCTCPPGFYGKVCE
LSAMTCADGPCFNGGRCSDNPDGGYTCHCPLGFSGFNCEKKMDLCGSSPCSNGAKCVDL
GNSYLCRCQAGFSGRYCEDNVDDCASSPCANGGTCRDSVNDFSCTCPPGYTGKNCSAPVS
RCEHAPCHNGATCHQRGQRYMCECAQGYGGPNCQFLLPEPPPGPMVVDLSERHMESQGG
PFPWVAVCAGVVLVLLLLLGCAAVVVCVRLKLQKHQPPPEPCGGETETMNNLANCQREK
DVSVSIIGATQIKNTNKKADFHGDHGAKKSSFKVRYPTVDYNLVRDLKGDEATVRDTHSK
RDTKCQSQSSAGEEKIAPTLRGGEIPDRKRPESVYSTSKDTKYQSVYVLSAEKDECVIATEV

Figure 4

CGGGCAGAGGTGGAAGAGGGGGGAGCGCCTCAAAGAAGCGATCAGAATAATAAAAGG
AGGCCGGGCTCTTTGCCTTCTGGAACGCGCGGCTCTTGAAAGGGCTTTTGAAAAGTAGT
GTTGTTTTCCAGTCGTGCATGCTCCAATCCACGGAGTATATTAGAGCCGGGACGCGGCG
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GCGGCGTCCGGAGTGCCCGTGGCGCGCGGCGCAGCGATGCGGTCCCCACGGACGCGCG
GCCGGCCCGGGCGCCCCCTGAGTCTTCTGCTCGCCCTGCTCTGTGCCCTGCGAGCCAAG
GTGTGCGGGGCCTCGGGTCAGTTTGAGCTGGAGATCCTGTCCATGCAGAACGTGAATG
GAGAGCTACAGAATGGGAACTGTTGTGGTGGAGTCCGGAACCCTGGCGACCGCAAGTG
CACCCGCGACGAGTGTGATACGTACTTCAAAGTGTGCCTCAAGGAGTATCAGTCCCGC
GTCACTGCCGGGGGACCCTGCAGCTTCGGCTCAGGGTCTACGCCTGTCATCGGGGGTA
ACACCTTCAATCTCAAGGCCAGCCGTGGCAACGACCGTAATCGCATCGTACTGCCTTTC
AGTTTCGCCTGGCCGAGGTCCTACACTTTGCTGGTGGAGGCCTGGGATTCCAGTAATGA
CACTATTCAACCTGATAGCATAATTGAAAAGGCTTCTCACTCAGGCATGATAAACCCTA
GCCGGCAATGGCAGACACTGAAACAAAACACAGGGATTGCCCACTTCGAGTATCAGAT
CCGAGTGACCTGTGATGACCACTACTATGGCTTTGGCTGCAATAAGTTCTGTCGTCCCA
GAGATGACTTCTTTGGACATTATGCCTGTGACCAGAACGGCAACAAAACTTGCATGGA
AGGCTGGATGGGTCCTGATTGCAACAAAGCTATCTGCCGACAGGGCTGCAGTCCCAAG
CATGGGTCTTGTAAACTTCCAGGTGACTGCAGGTGCCAGTACGGTTGGCAGGGCCTGT
ACTGCGACAAGTGCATCCCGCACCCAGGATGTGTCCACGGCACCTGCAATGAACCCTG
GCAGTGCCTCTGTGAGACCAACTGGGGTGGACAGCTCTGTGACAAAGATCTGAATTAC
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TGCTTGTCTCTCTGACCCCTGCCATAACCGAGGCAGCTGCAAGGAGACCTCCTCAGGCT
TTGAGTGTGAGTGTTCTCCAGGCTGGACTGGCCCCACGTGTTCCACAAACATCGATGAC
TGTTCTCCAAATAACTGTTCCCATGGGGGCACCTGCCAGGATCTGGTGAATGGATTCAA
GTGTGTGTGCCCGCCCCAGTGGACTGGCAAGACTTGTCAGTTAGATGCAAATGAGTGC
GAGGCCAAACCTTGTGTAAATGCCAGATCCTGTAAGAATCTGATTGCCAGCTACTACTG
TGATTGCCTTCCTGGCTGGATGGGTCAGAACTGTGACATAAATATCAATGACTGCCTTG
GCCAGTGTCAGAATGACGCCTCCTGTCGGGATTTGGTTAATGGTTATCGCTGTATCTGT
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CAGTGTATACGCTGGTAGACAGAGAGGAGAAGGCCCCCAGCGGCACGCCGACAAAAC
ACCCGAACTGGACAAATAAACAGGACAACAGAGACTTGGAAAGTGCCCAGAGCTTGA
ACCGGATGGAATACATCGTATAGCAGACAGTGGGCTGCCGCCATAGGTAGAGTTTGAG
GGCACCGCGGGCCG

Figure 5

CTGCGGCCGGCCCGCGAGCTAGGCTGGGTTTTTTTTTTCTCCCCTCCCTCCCCCCTTTT
TCCATGCAGCTGATCTAAAAGGGAATAAAAGGCTGCGCATAATCATAATAATAAAAGA
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AAAGAAGCGATCAGAATAATAAAAGGAGGCGGCTCTTTGCCTTCTGGAACGGGCCGCT
CTTGAAAGGGCTTTTGAAAAGTGGTGTTGTTTTCCAGTCGTGCATGCTCCAATCGGCGG
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GTGGAGGCGTGGGATTCCAGTAATGACACCGTTCAACCTGACAGTATTATTGAAAAGG
CTTCTCACTCGGGCATGATCAACCCCAGCCGGCAGTGGCAGACGCTGAAGCAGAACAC
GGGCGTTGCCCACTTTGAGTATCAGATCCGCGTGACCTGTGATGACTACTACTATGGCT
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CGTCCACGGCATCTGTAATGAGCCCTGGCAGTGCCTCTGTGAGACCAACTGGGGCGGC
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TTTTTTTTAATCTACTGCATTTAGGGAGTATTCTAATAAGCTAGTTGAATACTTGAACC
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TATTTATTAAATTTTTTTGTATGAAAACATGGAACAGTGTGGCTCTTCTGAGCTTACGTA
GTTCTACCGGCTTTGCCGTGTGCTTCTGCCACCCTGCTGAGTCTGTTCTGGTAATCGGGG
TATAATAGGCTCTGCCTGACAGAGGGATGGAGGAAGAACTGAAAGGCTTTTCAACCC
AAAACTCATCTGGAGTTCTCAAAGACCTGGGGCTGCTGTGAAGCTGGAACTGCGGGAG
CCCCATCTAGGGGAGCCTTGATTCCCTTGTTATTCAACAGCAAGTGTGAATACTGCTTG
AATAAACACCACTGGATTAATGGAAAAAAAAAAAAAAAA

Figure 6

MRSPRTRGRSGRPLSLLLALLCALRAKVCGASGQFELEILSMQNVNGELQNGNCCGGARN
PGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCSFGSGSTPVIGGNTFNLKASRGNDRNRIV
LPFSFAWPRSYTLLVEAWDSSNDTVQPDSIIEKASHSGMINPSRQWQTLKQNTGVAHFEYQ
IRVTCDDYYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPECNRAICRQGCSPK
HGSCKLPGDCRCQYGWQGLYCDKCIPHPGCVHGICNEPWQCLCETNWGGQLCDKDLNYC
GTHQPCLNGGTCSNTGPDKYQCSCPEGYSGPNCEIAEHACLSDPCHNRGSCKETSLGFECE
CSPGWTGPTCSTNIDDCSPNNCSHGGTCQDLVNGFKCVCPPQWTGKTCQLDANECEAKP
CVNAKSCKNLIASYYCDCLPGWMGQNCDININDCLGQCQNDASCRDLVNGYRCICPPGYA

NRASDYFCKCPEDYEGKNCSHLKDHCRTTPCEVIDSCTVAMASNDTPEGVRYISSNVCGPH
GKCKSQSGGKFTCDCNKGFTGTYCHENINDCESNPCRNGGTCIDGVNSYKCICSDGWEGA
YCETNINDCSQNPCHNGGTCRDLVNDFYCDCKNGWKGKTCHSRDSQCDEATCNNGGTCY
DEGDAFKCMCPGGWEGTTCNIARNSSCLPNPCHNGGTCVVNGESFTCVCKEGWEGPICAQ
NTNDCSPHPCYNSGTCVDGDNWYRCECAPGFAGPDCRININECQSSPCAFGATCVDEIN
GYRCVCPPGHSGAKCQEVSGRPCITMGSVIPDGAKWDDDCNTCQCLNGRIACSKVWCGPR
PCLLHKGHSECPSGQSCIPILDDQCFVHPCTGVGECRSSSLQPVKTKCTSDSYYQDNCANIT
FTFNKEMMSPGLTTEHICSELRNLNILKNVSAEYSIYIACEPSPSANNEIHVAISAEDIRDDGN
PIKEITDKIIDLVSKRDGNSSLIAAVAEVRVQRRPLKNRTDFLVPLLSSVLTVAWICCLVTAF
YWCLRKRRKPGSHTHSASEDNTTNNVREQLNQIKNPIEKHGANTVPIKDYENKNSKMSKIR
THNSEVEEDDMDKHQQKARFAKQPAYTLVDREEKPPNGTPTKHPNWTNKQDNRDLESAQ
SLNRMEYIV

Figure 7

GGAGCGGGCGCGCGGCGGCGGCGGGGCCGCGGCGGGCGGGTCGCGGGGGCAATGCGG
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CGGGCCGGCGCGACCAGGACCCGGGCTTCGTCGTCATCCCCTTCCAGTTCGCCTGGCCG
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CGATGGCTGCGGGTCAGACGCGGGGCCTGGGATGCCTGGCACAGCAGCCTCCGGCGTG
TGTGGCCCCCATGGACGCTGCGTCAGCCAGCCAGGGGGCAACTTTTCCTGCATCTGTGA
CAGTGGCTTTACTGGCACCTACTGCCATGAGAACATTGACGACTGCCTGGGCCAGCCCT
GCCGCAATGGGGGCACATGCATCGATGAGGTGGACGCCTTCCGCTGCTTCTGCCCCAG
CGGCTGGGAGGGCGAGCTCTGCGACACCAATCCCAACGACTGCCTTCCCGATCCCTGC

CACAGCCGCGGCCGCTGCTACGACCTGGTCAATGACTTCTACTGTGCGTGCGACGACG
GCTGGAAGGGCAAGACCTGCCACTCACGCGAGTTCCAGTGCGATGCCTACACCTGCAG
CAACGGTGGCACCTGCTACGACAGCGGCGACACCTTCCGCTGCGCCTGCCCCCCCGGC
TGGAAGGGCAGCACCTGCGCCGTCGCCAAGAACAGCAGCTGCCTGCCCAACCCCTGTG
TGAATGGTGGCACCTGCGTGGGCAGCGGGGCCTCCTTCTCCTGCATCTGCCGGGACGG
CTGGGAGGGTCGTACTTGCACTCACAATACCAACGACTGCAACCCTCTGCCTTGCTACA
ATGGTGGCATCTGTGTTGACGGCGTCAACTGGTTCCGCTGCGAGTGTGCACCTGGCTTC
GCGGGGCCTGACTGCCGCATCAACATCGACGAGTGCCAGTCCTCGCCCTGTGCCTACG
GGGCCACGTGTGTGGATGAGATCAACGGGTATCGCTGTAGCTGCCCACCCGGCCGAGC
CGGCCCCCGGTGCCAGGAAGTGATCGGGTTCGGGAGATCCTGCTGGTCCCGGGGCACT
CCGTTCCCACACGGAAGCTCCTGGGTGGAAGACTGCAACAGCTGCCGCTGCCTGGATG
GCCGCCGTGACTGCAGCAAGGTGTGGTGCGGATGGAAGCCTTGTCTGCTGGCCGGCCA
GCCCGAGGCCCTGAGCGCCCAGTGCCCACTGGGGCAAAGGTGCCTGGAGAAGGCCCC
AGGCCAGTGTCTGGACCACCCTGTGAGGCCTGGGGGAGTGCGGCGCAGAAGAGCCA
CCGAGCACCCCCTGCCTGCCACGCTCGGCCACCTGGACAATAACTGTGCCCGCCTCACC
TTGCATTTCAACCGTGACCACGTGCCCCAGGGCACCACGGTGGGCGCCATTTGCTCCGG
GATCCGCTCCCTGCCAGCCACAAGGGCTGTGGCACGGACCGCCTGCTGGTGTTGCTTT
GCGACCGGGCGTCCTCGGGGGCCAGTGCCGTGGAGGTGGCCGTGTCCTTCAGCCCTGC
CAGGGACCTGCCTGACAGCAGCCTGATCCAGGGCGCGGCCCACGCCATCGTGGCCGCC
ATCACCCAGCGGGGAACAGCTCACTGCTCCTGGCTGTCACCGAGGTCAAGGTGGAGAC
GGTTGTTACGGGCGGCTCTTCCACAGGTCTGCTGGTGCCTGTGCTGTGTGGTGCCTTCA
GCGTGCTGTGGCTGGCGTGCGTGGTCCTGTGCGTGTGGTGGACACGCAAGCGCAGGAA
AGAGCGGGAGAGGAGCCGGCTGCCGCGGGAGGAGAGCGCCAACACAGTGGGCCCCGC
TCAACCCCATCCGCAACCCCATCGAGCGGCCGGGGGGCCACAAGGACGTGCTCTACCA
GTGCAAGAACTTCACGCCGCCGCCGCGCAGGGCGGACGAGGCGCTGCCCGGGCCGGC
CGGCCACGCGGCGTCAGGGAGGATGAGGAGGACGAGGATCTGGGCCGCGGTGAGGAG
GACTCCCTGGAGGCGGAGAAGTTCTCTCACACAAATTCACCAAAGATCCTGGCCGCTC
GCCGGGGAGGCCGGCCCACTGGGCCTCAGGCCCCAAAGTGGACAACCGCGCGGTCAG
GAGCATCAATGAGGCCCGCTACGCCGGCAAGGAGTAGGGGCGGCTGCGCTGGGCCGG
GACCCAGGGCCCTCGGTGGGAGCCATGCCGTCTGCCGGACCCGGAGCCGAGGCATGTG
CTAGTTTCTTTATTTTGTGTAAAAAAACCACCAAAAACAAAAACCAAATGTTTATTTTC
TACGTTTCTTTAACCTTGTATAAATTATTCAGTAACTGTCAGGCTGAAAACAATGGAGT
ATTCTCGGATAGTTGCTATTTTTGTAAAGTTTCCGTGCGTGGCACTCGCTGTATGAAAG
GAGAGAGCAAAGGGTGTCTGCGTCGTCACCAAATCGTAGCGTTTGTTACCAGAGGTTG
TGCACTGTTTACAGAATCTTCCTTTTATTCCTCACTCGGGTTTCTCTGTGGCTCCAGGCC
AAAGTGCCGGTGAGACCCATGGCTGTGTTGGTGTGGCCCATGGCTGTTGGTGGGACC
CGTGGCTGATGGTGTGGCCTGTGGCTGTCGGTGGGACTCGTGGCTGTCAATGGGACCTG
TGGCTGTCGGTGGGACCTACGGTGGTCGGTGGGACCCTGGTTATTGATGTGGCCCTGGC
TGCCGGCACGGCCCGTGGCTGTTGACGCACCTGTGGTTGTTAGTGGGGCCTGAGGTCAT
CGGCGTGCCCAAGGCCGGCAGGTCAACCTCGCGCTTGCTGGCCAGTCCACCCTGCCTG
CCGTCTGTGCTTCCTCCTGCCCAGAACGCCCGCTCCAGCGATCTCTCCACTGTGCTTTCA
GAAGTGCCCTTCCTGCTGCGCAGTTCTCCCATCCTGGGACGGCGGCAGTATTGAAGCTC
GTGACAAGTGCCTTCACACAGACCCCTCGCAACTGTCCACGCGTGCCGTGGCACCAGG
CGCTGCCCACCTGCCGGCCCCGGCCGCCCCTCCTCGTGAAAGTGCATTTTTGTAAATGT
GTACATATTAAAGGAAGCACTCTGTATATTTGATTGAATAATGCCACCAAAAAAAAAA
AAAAAAAAAAATTCCTGCCC

Figure 8

MRAQGRGAFPPALLLLLALWVQAARPMGYFELQLSALRNVNGELLSGACCDGDGRTTRA

PRAGGDQDPGFVVIPFQFAWPRSFTLIVEAWDWDNDTTPNEELLIERVSHAGMINPEDRWK
SLHFSGHVAHLELQIRVRCDENYYSATCNKFCRPRNDFFGHYTCDQYGNKACMDGWMG
KECKEAVCKQGCNLLHGGCTVPGECRCSYGWQGRFCDECVPPGCVHGSCVEPWQCNCET
NWGGLLCDKDLNYCGSHHPCTNGGTCINAEPDQYRCTCPDGYSGRNCEKAEHACTSNPC
ANGGSCHEVPSGFECHCPSGWSGPTCALDIDECASNPCAAGGTCVDQVDGFECICPEQWV
GATCQLDVNDCEGKPCLNAFSCKNLIGGYYCDCIPGWKGINCHINVNDCRGQCQHGGTCK
DLVNGYQCVCPRGFGGRHCELERDKCASSPCHSGGLCEDLADGFHCHCPQGFSGPLCEVD
VDLCEPSPCRNGARCYNLEGDYYCACPDDFGGKNCSVPREPCPGGACRVIDGCGSDAGPG
MPGTAASGVCGPHGRCVSQPGGNFSCICDSGFTGTYCHENIDDCLGQPCRNGGTCIDEVDA
FRCFCPSGWEGELCDTNPNDCLPDPCHSRGRCYDLVNDFYCACDDGWKGKTCHSREFQC
DAYTCSNGGTCYDSGDTFRCACPPGWKGSTCAVAKNSSCLPNPCVNGGTCVGSGASFSCI
CRDGWEGRTCTHNTNDCNPLPCYNGGICVDGVNWFRCECAPGFAGPDCRINIDECQSSPC
AYGATCVDEINGYRCSCPPGRAGPRCQEVIGFGRSCWSRGTPFPHGSSWVEDCNSCRCLDG
RRDCSKVWCGWKPCLLAGQPEALSAQCPLGQRCLEKAPGQCLRPPCEAWGECGAEEPPST
PCLPRSGHLDNNCARLTLHFNRDHVPQGTTVGAICSGIRSLPATRAVARDRLLVLLCDRAS
SGASAVEVAVSFSPARDLPDSSLIQGAAHAIVAAITQRGNSSLLLAVTEVKVETVVTGGSST
GLLVPVLCGAFSVLWLACVVLCVWWTRKRRKERERSRLPREESANNQWAPLNPIRNPIER
PGGHKDVLYQCKNFTPPPRRADEALPGPAGHAAVREDEEDEDLGRGEEDSLEAEKFLSHK
FTKDPGRSPGRPAHWASGPKVDNRAVRSINEARYAGKE

Figure 9

MRSPRTRGRPGRPLSLLLALLCALRAKVCGASGQFELEILSMQNVNGELQNGNCCGGVRN
PGDRKCTRDECDTYFKVCLKEYQSRVTAGGPCSFGSGSTPVIGGNTFNLKASRGNDRNRIV
LPFSFAWPRSYTLLVEAWDSSNDTIQPDSIIEKASHSGMINPSRQWQTLKQNTGIAHFEYQIR
VTCDDHYYGFGCNKFCRPRDDFFGHYACDQNGNKTCMEGWMGPDCNKAICRQGCSPKH
GSCKLPGDCRCQYGWQGLYCDKCIPHPGCVHGTCNEPWQCLCETNWGGQLCDKDLNYC
GTHQPCLNRGTCSNTGPDKYQCSCPEGYSGPNCEIAEHACLSDPCHNRGSCKETSSGFECE
CSPGWTGPTCSTNIDDCSPNNCSHGGTCQDLVNGFKCVCPPQWTGKTCQLDANECEAKPC
VNARSCKNLIASYYCDCLPGWMGQNCDININDCLGQCQNDASCRDLVNGYRCICPPGYAG
DHCERDIDECASNPCLNGGHCQNEINRFQCLCPTGFSGNLCQLDIDYCEPNPCQNGAQCYN
RASDYFCKCPEDYEGKNCSHLKDHCRTTTCEVIDSCTVAMASNDTPEGVRYISSNVCGPHG
KCKSQSGGKFTCDCNKGFTGTYCHENINDCESNPCKNGGTCIDGVNSYKCICSDGWEGAH
CENNINDCSQNPCHYGGTCRDLVNDFYCDCKNGWKGKTCHSRDSQCDEATCNNGGTCY
DEVDTFKCMCPGGWEGTTCNIARNSSCLPNPCHNGGTCVVNGDSFTCVCKEGWEGPICTQ
NTNDCSPHPCYNSGTCVDGDNWYRCECAPGFAGPDCRININECQSSPCAFGATCVDEINGY
QCICPPGHSGAKCHEVSGRSCITMGRVILDGAKWDDDCNTCQCLNGRVACSKVWCGPRPC
RLHKSHNECPSGQSCIPVLDDQCFVRPCTGVGECRSSSLQPVKTKCTSDSYYQDNCANITFT
FNKEMMSPGLTTEHICSELRNLNILKNVSAEYSIYIACEPSLSANNEIHVAISAEDIRDDGNP
VKEITDKIIDLVSKRDGNSSLIAAVAEVRVQRRPLKNRTDFLVPLLSSVLTVAWVCCLVTAF
YWCVRKRRKPSSHTHSAPEDNTTNNVREQLNQIKNPIEKHGANTVPIKDYENKNSKMSKIR
THNSEVEEDDMDKHQQKVRFAKQPVYTLVDREEKAPSGTPTKHPNWTNKQDNRDLESAQ
SLNRMEYIV

Figure 10

TCGAGGCGGCGATGCGGGCACGCGGCTGGGGACGCCTGCCTCGGCGGCTGCTGCTGCT

GCGCTGCGGAACGTGAACGGGGAGCTGCTGAGCGGCGCCTGCTGTGACGGCGACGGC
CGGACGACGCGCGCGGGGGGCTGCGGCCGCGACGAGTGCGACACGTACGTGCGCGTG
TGCCTTAAGGAGTACCAGGCCAAGGTGACGCCCACGGGGCCCTGCAGCTACGGCTACG
GCGCCACGCCCGTGCTGGGTGGCAACTCCTTCTACCTGCCGCCGGCGGGCGCTGCGGG
GGACCGAGCGCGCGCGCGGTCTCGGACCGGCGGCCACCAGGACCCGGGCCTCGTCGTC
ATTCCCTTTCAGTTCGCCTGGCCGCGTTCTTTCACCCTCATCGTGGAGGCCTGGGACTG
GGACAATGACACCACTCCAGATGAGGAGCTGCTGATTGAGCGGGTGTCGCACGCTGGC
ATGATCAACCCCGAGGACCGCTGGAAGAGCCTGCACTTCAGCGGCCACGTGGCACACC
TGGAGCTGCAGATCCGAGTGCGCTGTGATGAGAACTACTACAGTGCCACCTGCAACAA
GTTCTGCCGGCCCCGCAACGACTTCTTTGGCCACTATACCTGCGACCAGTACGGCAACA
AGGCCTGCATGGATGGCTGGATGGGCAAAGAATGCAAAGAAGCCGTGTGTAAACAAG
GATGTAATTTGCTCCACGGGGGATGCACTGTGCCTGGGGAGTGCAGGTGCAGCTACGG
CTGGCAGGGCAAGTTCTGTGACGAGTGTGTCCCCTACCCTGGCTGCGTGCATGGCAGCT
GTGTGGAGCCCTGGCACTGTGACTGTGAGACCAACTGGGGTGGCCTGCTCTGCGACAA
AGACCTGAACTACTGTGGCAGCCACCACCCCTGTGTCAACGGGGGTACCTGCATCAAT
GCTGAGCCTGACCAATACCTCTGCGCCTGCCCAGATGGCTACTTGGGCAAGAACTGTG
AGCGGGCTGAGCACGCCTGTGCCTCCAACCCGTGTGCCAATGGGGGCTCTTGCCACGA
AGTGCCATCTGGCTTTGAATGCCACTGTCCGTCAGGATGGAGCGGACCCACCTGTGCG
CTCGACATTGATGAGTGTGCCTCTAACCCATGTGCAGCGGGTGGTACCTGCGTGGATCA
GGTGGACGGCTTCGAGTGCATCTGCCCGGAGCAGTGGGTGGGGGCTACTTGCCAGCTG
GACGCCAATGAGTGTGAAGGGAAGCCGTGCCTTAATGCTTTTTCTTGCAAAAACCTGAT
TGGCGGCTATTACTGTGATTGCCTCCCGGGCTGGAAGGGCATCAACTGCCAAATCAAC
ATCAACGATTGTCATGGGCAGTGTCAGCATGGGGGCACCTGCAAGGACCTGGTCAATG
GGTACCAGTGTGTGTGCCCGCGGGGCTTTGGAGGTCGCCATTGCGAACTAGAGTACGA
CAAGTGTGCCAGCAGCCCCTGCCGCCGGGGTGGCATCTGCGAGGACCTGGTGGATGGC
TTCCGCTGCCACTGCCCACGGGGCCTCTCTGGGCTGCACTGTGAGGTGGACATGGATCT
CTGTGAACCAAGCCCCTGCCTCAACGGTGCTCGCTGCTACAACCTTGAGGGTGACTACT
ACTGCGCCTGCCCAGAAGACTTTGGTGGCAAGAACTGCTCAGTGCCCAGGGACACATG
CCCTGGCGGGGCATGTAGAGTGATCGATGGCTGCGGGTTCGAGGCAGGGTCCAGGGCA
CGCGGTGTCGCACCCTCTGGTATATGTGGCCCTCACGGGCACTGCGTTAGCCTGCCTGG
GGGAAACTTCTCCTGCATCTGTGACAGCGGCTTCACAGGCACCTACTGCCATGAAAAC
ATTGACGACTGCATGGGCCAGCCCTGCCGCAACGGGGGCACGTGCATTGACGAAGTGG
ACTCCTTCCGCTGCTTCTGCCCCAGTGGCTGGGAAGGAGAACTCTGTGACATCAATCCC
AACGACTGCCTCCCCGACCCCTGCCACAGCCGCGGCCGCTGCTATGACCTGGTCAATG
ACTTCTACTGTGCCTGTGACGATGGCTGGAAGGGCAAGACCTGCCACTCACGCGAGTT
CCAGTGTGACGCCTACACCTGCAGCAACGGTGGCACATGCTATGACAGCGGCGACACC
TTCCGCTGCGCGTGCCCTCCGGGCTGGAAGGGCAGCACCTGCACCATCGCCAAGAACA
GCAGCTGTGTGCCCAATCCCTGTGTGAATGGAGGCACCTGCGTGGGTAGCGGAGACTC
TTTCTCCTGCATCTGCCGGGATGGCTGGGAGGGCCGCACCTGCACACATAACACCAAT
GACTGCAACCCTCTGCCCTGCTATAACGGAGGCATCTGTGTTGATGGCGTCAACTGGTT
CCGCTGCGAGTGTGCGCCTGGCTTTGCGGGTCCTGACTGCCGTATCAACATTGATGAGT
GCCAGTCCTCGCCCTGTGCCTACGGAGCCACGTGTGTGGATGAGATCAACGGGTACCG
CTGCAGCTGCCCACCAGGTCGTTCTGGCCCCAGGTGCCAGGAAGTGGTCATATTCACG
AGGCCCTGCTGGTCCCGGGGAATGTCCTTCCCGCATGGGAGTTCCTGGATGGAAGACT
GCAACAGCTGCCGCTGCCTGGATGGCCACCGGGATTGTAGCAAGGTATGGTGCGGATG
GAAGCCTTGCCTGCTCTCTGGTCAGCCCAGCGATCCGAGTGCCCAGTGCCCCCCAGGG
CAGCAATGTCAGGAGAAGGCCGTGGGTCAGTGCTTGCAGCCACCCTGTGAGAACTGGG
GGGAGTGTACAGCGGAGGAGCCTCTGCCACCCAGCACCCCCTGTCAGCCACGGAGCAG
TCATTTGGACAACAACTGTGCCCGACTCACACTGCGCTTCAACCGTGATCAAGTGCCTC
AGGGCACCACCGTGGGCGCTATCTGCTCTGGAATCCGAGCCTTGCCTGCCACGAGGGC
GGCGGCACACGACCGCCTCCTCCTGCTGCTTTGTGATCGAGCATCCTCGGGGGCCAGTG
[illegible]TTTGAGCCCTGCAAGGGACCTGCCTGACAGCAGCCTGATC

CAGAGCACAGCCCACGCCATCGTGGCTGCTATCACTCAGAGAGGAAATAGCTCACTGC
TGCTGGCTGTCACCGAGGTCAAGGTGGAAACAGTTGTTATGGGTGGCTCTTCCACAGGT
CTGTTGGTGCCCGTGCTGTGCAGCGTGTTCAGTGTGCTGTGGCTCGCCTGTGTGGTTAT
CTGCGTATGGTGGACACGAAAGCGCAGGAAAGAACGTGAGAGGAGCCGGCTACCACG
GGATGAGAGCACCAACAACCAGTGGCCCCGCTCAATCCCATCCGCAACCCCATTGAG
CGGCCAGGCGGCAGCGGTCTGGGAACTGGGGGCCACAAGGACATACTCTACCAGTGC
AAAAACTTCACACCGCCGCCCCGCAGGGCAGGCGAGGCACTGCCCGGGCCAGCTGGCC
ATGGGGCTGGTGGGGAGGACGAGGAGGATGAAGAGCTGAGCCGTGGAGATGGGGACT
CCCCAGAGGCAGAGAAGTTCATCTCACACAAGTTCACCAAAGACCCCAGCTGCTCCCT
CGGAAGGCCAGCCTGCTGGGCTCCAGGGCCCAAAGTGGACAACCGCGCCGTCAGAAG
TACCAAGGACGTGCGCCGTGCTGGCAGGGAGTAGCCAGCCACCAGGCTGGCACCCAG
AACCCTTGCTGGCACCACGCTGCCTGCCGGACCATAGGAGGCCAAGGCCGTGTGCATA
GTTTCTTTATTTTGTGTAAAAAACAAAACCAAAACCAAAAAACAAATGTTTATTTTTTA
CGTTTCTTTAACCTTGTATAAATTATTCAACGGCTGTCAGGCGGAAAACAACGGAGTAT
TCTCGGATCATTGCTATTTTTGTAAAGTTTCCGCGTCCGCACGCACTGTGGCAGGAGAG
CAGGGCGTGTGTATGTGTGTGTGTGTGTGTCCTCACC

Figure 11

MLCDKDLNYCGSHHPCVNGGTCINAEPDQYLCACPDGYLGKNCERAEHACASNPCANGG
SCHEVPSGFECHCPSGWSGPTCALDIDECASNPCAAGGTCVDQVDGFECICPEQWVGATC
QLDANECEGKPCLNAFSCKNLIGGYYCDCLPGWKGINCQITINDCHGQVSAWGHLQGPVN
GYQCVCPRGFGVRHCELEYDKCASSPCRRGGICEDLVDGFRCHCPRGLSGLHCEVDMDLC
EPSPCFNGVRCYNLEGDYYCACPEDFGGKNCSVPRDTCPGGACRVIDGCGFEAGSRARGV
APSGICGPHGHCVSLPGGNFSCICDSGFTGTYCHENIDDCMGQPCRNGGTCIDEVDSFRCFC
PSGWEGELCDINPNDCLPDPCHSRGRCYDLVNDFYCACDDGWKGKTCHSREFQCDAYTC
SNGGTCYDSGDTFRCACPPGWKGSTCTIAKNSSCVPNPCVNGGTCVGSGDSFSCICRDGWE
GRTCTHNTNDCNPLPCYNGGICVDGVHWFACECAPGF

Figure 12

GAAGGCCATGGTCTCCCCACGGATGTCCGGGCTCCTCTCCCAGACTGTGATCCTAGCGC
TCATTTTCCTCCCCCAGACACGGCCCGCTGGCGTCTTCGAGCTGCAGATCCACTCTTTC
GGGCCGGGTCCAGGCCCTGGGGCCCCGCGGTCCCCCTGCAGCGCCCGGCTCCCCTGCC
GCCTCTTCTTCAGAGTCTGCCTGAAGCCTGGGCTCTCAGAGGAGGCCGCCGAGTCCCCG
TGCGCCCTGGGCGCGGCGCTGAGTGCGCGCGGACCGGTCTACACCGAGCAGCCCGGAG
CGCCCGCGCCTGATCTCCCACTGCCCGACGGGCTCTTGCAGGTGCCCTTCCGGGACG
CCTGGCCTGGCACCTTCTCTTTCATCATCGAAACCTGGAGAGAGGAGTTAGGAGACCA
GATTGGAGGGCCCGCCTGGAGCCTGCTGGCGCGCGTGGCTGGCAGGCGGCGCTTGGCA
GCCGGAGGCCCGTGGGCCCGGGCATTCAGCGCGCAGGCGCCTGGGAGCTGCGCTTCTC
GTACCGCGCGCGCTGCGAGCCGCCTGCCGTCGGGACCGCGTGCACGCGCCTCTGCCGT
CCGCGCAGCGCCCCCTCGCGGTGCGGTCCGGGACTGCGCCCCTGCGCACCGCTCGAGG
ACGAATGTGAGGCGCCGCTGGTGTGCCGAGCAGGCTGCAGCCCTGAGCATGGCTTCTG
TGAACAGCCCGGTGAATGCCGATGCCTAGAGGGCTGGACTGGACCCCTCTGCACGGTC
CCTGTCTCCACCAGCAGCTGCCTCAGCCCCAGGGGCCCGTCCTCTGCTACCACCGGATG
CCTTGTCCCTGGGCCTGGGCCCTGTGACGGGAACCCGTGTGCCAATGGAGGCAGCTGT
AGTGAGACACCCAGGTCCTTTGAATGCACCTGCCCGCGTGGGTTCTACGGGCTGCGGT

GCTTGTGTGTCGGGGGTGCAGACCCTGACTCTGCCTACATCTGCCACTGCCCACCTGGT
TTCCAAGGCTCCAACTGTGAGAAGAGGGTGGACCGGTGCAGCCTGCAGCCATGCCGCA
ATGGCGGACTCTGCCTGGACCGGGCCACGCCCTGCGCTGCCGCTGCCGCGCCGGCTTC
GCGGGTCCTCGCTGCGAGCACGACCTGGACGACTGCGCGGGCCGCGCCTGCGCTAACG
GCGGCACGTGTGTGGAGGGCGGCGGCGCGCACCGCTGCTCCTGCCGCTGGGCTTCGGC
GGCCGCGACTGCCGCGAGCGCGCGGACCCGTGCGCCGCGCGCCCCTGTGCTCACGGC
GGCCGCTGCTACGCCCACTTCTCCGGCCTCGTCTGCGCTTGCGCTCCCGGCTACATGGG
AGCGCGGTGTGAGTTCCCAGTGCACCCCGACGGCGCAAGCGCCTTGCCCGCGGCCCCG
CCGGGCCTCAGGCCCGGGGACCCTCAGCGCTACCTTTTGCCTCCGGCTCTGGGACTGCT
CGTGGCCGCGGGCGTGGCCGGCGCTGCGCTCTTGCTGGTCCACGTGCGCCGCCGTGGC
CACTCCCAGGATGCTGGGTCTCGCTTGCTGGCTGGGACCCCGGAGCCGTCAGTCCACG
CACTCCCGGATGCACTCAACAACCTAAGGACGCAGGAGGGTTCCGGGGATGGTCCGG
CTCGTCCGTAGATTGGAATCGCCCTGAAGATGTAGACCCTCAAGGGATTTATGTCATAT
CTGCTCCTTCCATCTACGCTCGGGAGGTAGCGACGCCCCTTTTCCCCCCGCTACACACT
GGGCGCGCTGGGCAGAGGCAGCACCTGCTTTTTCCCTACCCTTCCTCGATTCTGTCCGT
GAAATGAATTGGGTAGAGTCTCTGGAAGGTTTTAAGCCCATTTTCAGTTCTAACTTACT
TTCATCCTATTTTGCATCCCTCTTATCGTTTTGAGCTACCTGCCATCTTCTCTTT

Figure 13

MVSPRMSGLLSQTVILALIFLPQTRPAGVFELQIHSFGPGPGPGAPRSPCSARLPCRLFFRVC
LKPGLSEEAAESPCALGAALSARGPVYTEQPGAPAPDLPLPDGLLQVPFRDAWPGTFSFIIE
TWREELGDQIGGPAWSLLARVAGRRRLAAGGPWARDIQRAGAWELRFSYRARCEPPAVG
TACTRLCRPRSAPSRCGPGLRPCAPLEDECEAPLVCRAGCSPEHGFCEQPGECRCLEGWTG
PLCTVPVSTSSCLSPRGPSSATTGCLVPGPGPCDGNPCANGGSCSETPRSFECTCPRGFYGLR
CEVSGVTCADGPCFNGGLCVGGADPDSAYICHCPPGFQGSNCEKRVDRCSLQPCRNGGLC
LDLGHALRCRCRAGFAGPRCEHDLDDCAGRACANGGTCVEGGGAHRCSCALGFGGRDCR
ERADPCAARPCAHGGRCYAHFSGLVCACAPGYMGARCEFPVHPDGASALPAAPPGLRPG
DPQRYLLPPALGLLVAAGVAGAALLLVHVRRRGHSQDAGSRLLAGTPEPSVHALPDALNN
LRTQEGSGDGPSSSVDWNRPEDVDPQGIYVISAPSIYAREVATPLFPPLHTGRAGQRQHLLF
PYPSSILSVK

Figure 14

AAACCGGAACGGGGCCCAACTTCTGGGGCCTGGAGAAGGGAAACGAAGTCCCCCCCG
GTTTCCCGAGGTGCCTTTCCTCGGGCATCCTTGGTTTCGGCGGGACTTCGCAGGGCGGA
TATAAAGAACGGCGCCTTTGGGAAGAGGCGGAGACCGGCTTTAAAGAAAGAAGTCTTG
GTCCTGCGGCTTGGGCGAGGCAAGGGCGAGGCAGGGCGCTTTCTGCCGACGCTCCCCG
TGGCCCTACGATCCCCCGCGCGTCCGCCGCTGTTCTAAGGAGAGAAGTGGGGGCCCCC
CAGGCTCGCGCGTGGAGCGAAGCAGCATGGGCAGTCGGTGCGCGCTGGCCCTGGCGT
GCTCTCGGCCTTGCTGTGTCAGGTCTGGAGCTCTGGGGTGTTCGAACTGAAGCTGCAGG
AGTTCGTCAACAAGAAGGGGCTGCTGGGGAACCGCAACTGCTGCCGCGGGGGCGCGG
GGCCACCGCCGTGCGCCTGCCGACCTTCTTCCGCGTGTGCCTCAAGCACTACCAGGCCA
GCGTGTCCCCCGAGCCGCCCTGCACCTACGGCAGCGCCGTCACCCCCGTGCTGGGCGT
CGACTCCTTCAGTCTGCCCGACGGCGGGGGCGCCGACTCCGCGTTCAGCAACCCCATC
CGCTTCCCCTTCGGCTTCACCTGGCCGGGCACCTTCTCTCTGATTATTGAAGCTCTCC
ACACAGATTCTCCTGATGACCTCGCAACAGAAAACCCAGAAAGACTCATCAGCCGCCT
GGCCACCCAGAGGCACCTGACGGTGGGCGAGGAGTGGTCCCAGGACCTGCACAGCAG
CGGCCGCACGGACCTCAAGTACTCTACCGCTTCGTGTGTGACGAACACTACTACGGAG
AGGGCTGCTCCGTTTTCTGCCGTCCCCGGGACGATGCCTTCGGCCACTTCACCTGTGGG

ATCTGCCTGCCTGGATGTGATGAGCAGCATGGATTTTGTGACAAACCAGGGGAATGCA
AGTGCAGAGTGGGCTGGCAGGGCCGGTACTGTGACGAGTGTATCCGCTATCCAGGCTG
TCTCCATGGCACCTGCCAGCAGCCCTGGCAGTGCAACTGCCAGGAAGGCTGGGGGGGC
CTTTTCTGCAACCAGGACCTGAACTACTGCACACACCATAAGCCCTGCAAGAATGGAG
CCACCTGCACCAACACGGGCCAGGGGAGCTACACTTCTCTTGCCGGCCTGGGTACACA
GGTGCCACCTGCGAGCTGGGGATTGACGAGTGTGACCCCAGCCCTTGTAAGAACGGAG
GGAGCTGCACGGATCTCGAGAACAGCTACTCCTGTACCTGCCCACCCGGCTTCTACGG
CAAAATCTGTGAATTGAGTGCCATGACCTGTGCGGACGGCCCTTGCTTTAACGGGGGTC
GGTGCTCAGACAGCCCCGATGGAGGGTACAGCTGCCGCTGCCCCGTGGGCTACTCCGG
CTTCAACTGTGAGAAGAAAATTGACTACTGCAGCTCTTCACCCTGTTCTAATGGTGCCA
AGTGTGTGGACCTCGGTGATGCCTACCTGTGCCGCTGCCAGGCCGGCTTCTCGGGGAG
GCACTGTGACGACAACGTGGACGACTGCGCCTCCTCCCCGTGCGCCAACGGGGGCACC
TGCCGGGATGGCGTGAACGACTTCTCCTGCACCTGCCCGCCTGGCTACACGGGCAGGA
ACTGCAGTGCCCCCGTCAGCAGGTGCGAGCACGCACCCTGCCACAATGGGGCCACCTG
CCACCAGAGGGGCACGGCTATGTGTGCGAATGTGCCCGAAGCTACGGGGGTCCCAACT
GCCAGTTCCTGCTCCCCGAGCTGCCCCCGGGCCCAGCGGTGGTGGACCTCACTGAGAA
GCTAGAGGGCCAGGGCGGGCCATTCCCCTGGGTGGCGTGTGCGCCGGGGTCATCCTTG
TCCTCATGCTGCTGCTGGGCTGTGCCGCTGTGGTGGTCTGCGTCCGGCTGAGGCTGCAG
AAGCACCGGCCCCCAGCCGACCCCTGCCGGGGGGAGACGGAGACCATGAACAACCTG
GCAACTGCCAGCGTGAGAAGGACATCTCAGTCAGCATCATCGGGGCCACGCAGATCAA
GAACACCAACAAAAGGCGGACTTCCACGGGGACCACAGCGCCGACAAGAATGGCTTC
AAGGCCCGCTACCCAGCGGTGGACATAACCTCGTGCAGGACCTCAAGGGTGACGACAC
CGCCGTCAGGGACGCGCACAGCAAGCGTGACACCAGTGCCAGCCCCAGGGCTCCTCAG
GGGAGGAGAAGGGGACCCCGACCACACTCAGGGGTGGAGAAGCATCGAAAGAAAAA
GGCCGGACTCGGGCTGTTCAACTTCAAAAGACACCAAGTACCAGTCGGTGTACGTCAT
ATCCGAGGAGAAGGATGAGTGCGTCATAGCAACTGAGGTGTAAAATGGAAGTGAGAT
GGCAAGACTCCCGTTCTCTTAAAATAAGTAAAATTCCAAGGATATATGCCCCAACGAA
TGCTGCTGAAGAGGAGGGAGGCCTCGTGGACTGCTGCTGAGAAACCGAGTTCAGACCG
AGCAGGTTCTCCTCCTGAGGTCCTCGACGCCTGCCGACAGCCTGTCGCGGCCCGGCCGC
CTGCGGCACTGCCTTCCGTGACGTCGCCGTTGCACTATGGACAGTTGCTCTTAAGAGAA
TATATATTTAAATGGGTGAACTGAATTACGCCTAAGAAGCATGCACTGCCTGAGTGTAT
ATTTTGGATTCTTATGAGCCAGTCTTTTCTTGAATTAGAAACACAAACACTGCCTTTATT
GTCCTTTTTGATACGAAGATGTGCTTTTTCTAGATGGAAAAGATGTGTGTTATTTTTTGG
ATTTGTAAAAATATTTTTCATGATATCTGTAAAGCTTGAGTATTTTGTGATGTTCGTTTT
TTATAATTTAAATTTTGGTAAATATGTACAAAGGCACTTCGGGTCTATGTGACTATATT
TTTTTGTATATAAATGTATTTATGGAATATTGTGCCAATGTTATTTGAGTTTTTTACTGT
TTTGTTAATGAAGAAATTCCTTTTTAAAATATTTTTCCAAAATAAATTTTATGAGGAATT
C

Figure 15

MGSRCALALAVLSALLCQVWSSGVFELKLQEFVNKKGLLGNRNCCRGGAGPPPCACRTFF
RVCLKHYQASVSPEPPCTYGSAVTPVLGVDSFSLPDGGGADSAFSNPIRFPFGFTWPGTFSLI
IEALHTDSPDDLATENPERLISRLATQRHLTVGEEWSQDLHSSGRTDLKYSYRFVCDEHYY
GEGCSVFCRPRDDAFGHFTCGERGEKVCNPGWKGPYCTEPICLPGCDEQHGFCDKPGECK
CRVGWQGRYCDECIRYPGCLHGTCQQPWQCNCQEGWGGLFCNQDLNYCTHHKPCKNGA
TCTNTGQGSYTCSCRPGYTGATCELGIDECDPSPCKNGGSCTDLENSYSCTCPPGFYGKICE
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CEHAPCHNGATCHQRGHGYVCECARSYGGPNCQFLLPELPPGPAVVDLTEKLEGQGGPFP
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VSIIGATQIKNTNKKADFHGDHSADKNGFKARYPAVDYNLVQDLKGDDTAVRDAHSKRD
TKCQPQGSSGEEKGTPTTLRGGEASERKRPDSGCSTSKDTKYQSVYVISEEKDECVIATEV

Figure 16

ATGGCGGCAGCGTCCCGGAGCGCCTCTGGCTGGGCGCTACTGCTGCTGGTGGCACTTT
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GTCTCCACGCCGGTATTGGGCACCAACTCCTTCGCTGTCCGGGACGACAGTAGCGGCG
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GATGCACTCATCAGCAAGATCGCCATCCAGGGCTCCCTAGCTGTGGGTCAGAACTGGT
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AGTGACAACTACTATGGAGACAACTGCTCCCGCCTGTGCAAGAAGCGCAATGACCACT
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GAATATTGCCAACAGCCTATCTGTCTTTCGGGCTGTCATGAACAGAATGGCTACTGCA
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TGTCGCCCAGGCTACACTGGTGTGGACTGTGAGCTGGAGCTCAGCGAGTGTGACAGCA
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Figure 17

MAAASRSASGWALLLLVALWQQRAAGSGVFQLQLQEFINERGVLASGRPCEPGCRTFFRV
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GPSRMCRCRPGFTGTYCELHVSDCARNPCAHGGTCHDLENGLMCTCPAGFSGRRCEVRTS
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VLLGMVAVAVRQLRLRRPDDGSREAMNNLSDFQKDNLIPAAQLKNTNQKKELEVDCGLD
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DSMYQSVCLISEERNECVIATEV

Figure 18

CTCGCAGGCTAGGAACCCGAGGCCAAGAGCTGCAGCCAAAGTCACTTGGGTGCAGTGT
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CTGCGGCTGCAGGAGTTCGTCAACCAGCGCGGTATGCTGGCCAATGGGCAGTCCTGCG
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Figure 19

MTPASRSACRWALLLLAVLWPQQRAAGSGIFQLRLQEFVNQRGMLANGQSCEPGCRTFFR
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WQGRLCNECIPHNGCRHGTCSIPWQCACDEGWGGLFCDQDLNYCTHHSPCKNGSTCSNS
GPKGYTCTCLPGYTGEHCELGLSKCASNPCRNGGSCKDQENSYHCLCPPGYYGQHCEHST
LTCADSPCFNGGSCRERNQGSSYACECPPNFTGSNCEKKVDRCTSNPCANGGQCLNRGPSR
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SGPCFNGATCYTGLSPNNFVCNCPYGFVGSRCEFPVGLPPSFPWVAVSLGVGLVVLLVLLV
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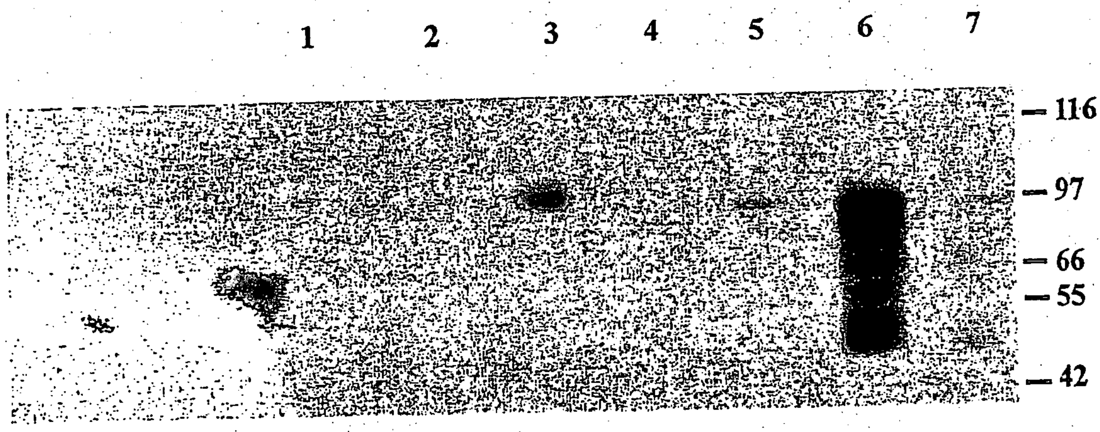
Figure 20



Western blot analysis of Notch 2 expression in human germ cell tumour derived cell lines.

Western blot probed with antibody specific for the intracellular portion of human NOTCH2 and visualised using chemilumenesence. Lanes from left to right 1: BeWo, 2: TERA-1, 3: 833KE, 4: 2102 Ep 2A6, 5: 2102 Ep 4D3, 6: NTERA2/D1 8 days exposure to retinoic acid, 7: NTERA2/D1 EC cells. Molecular weight markers are indicated on the right in kDa. Notch2 protein product is visualized at apprx 100 kDa

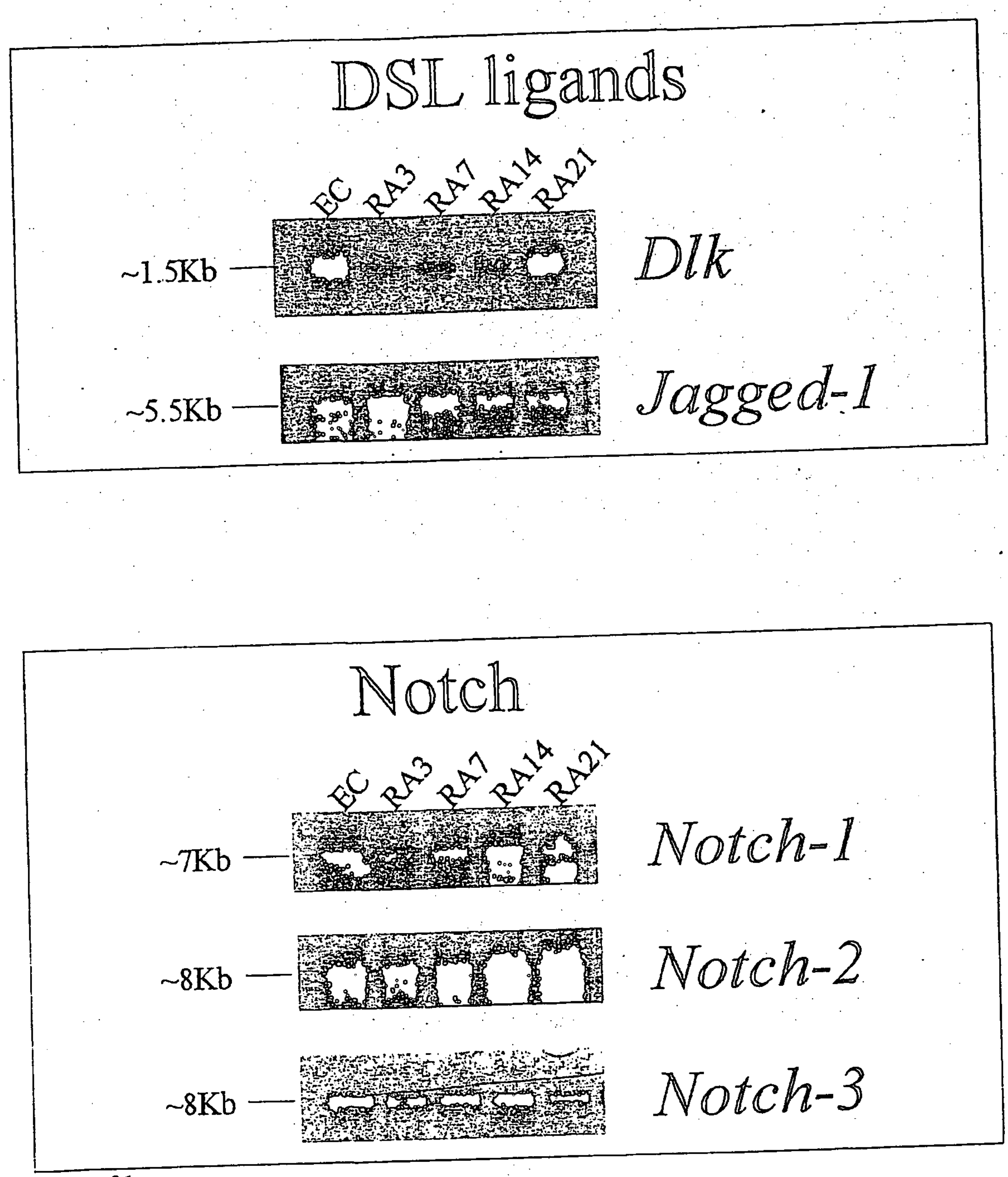

DSL ligands
EC
RA3
RA7
RA14
RA21
~1.5Kb
Dlk
~5.5Kb
Jagged-1
Notch
EC
RA3
RA7
RA14
RA21
~7Kb
Notch-1
~8Kb
Notch-2
~8Kb
Notch-3

Figure 21

Figure 22

AAACCCACTCCACCTTACTACCAGACAACCTTAGCCAAACCATTTACCCAAATAAAGT
ATAGGCGATAGAAATTGAAACCTGGCGCAATAGATATAGTACCGCAAGGGAAAGATG
AAAAATTATAACCAAGCATAATATAGCAAGGACTAACCCCTATACCTTCTGCATAATG
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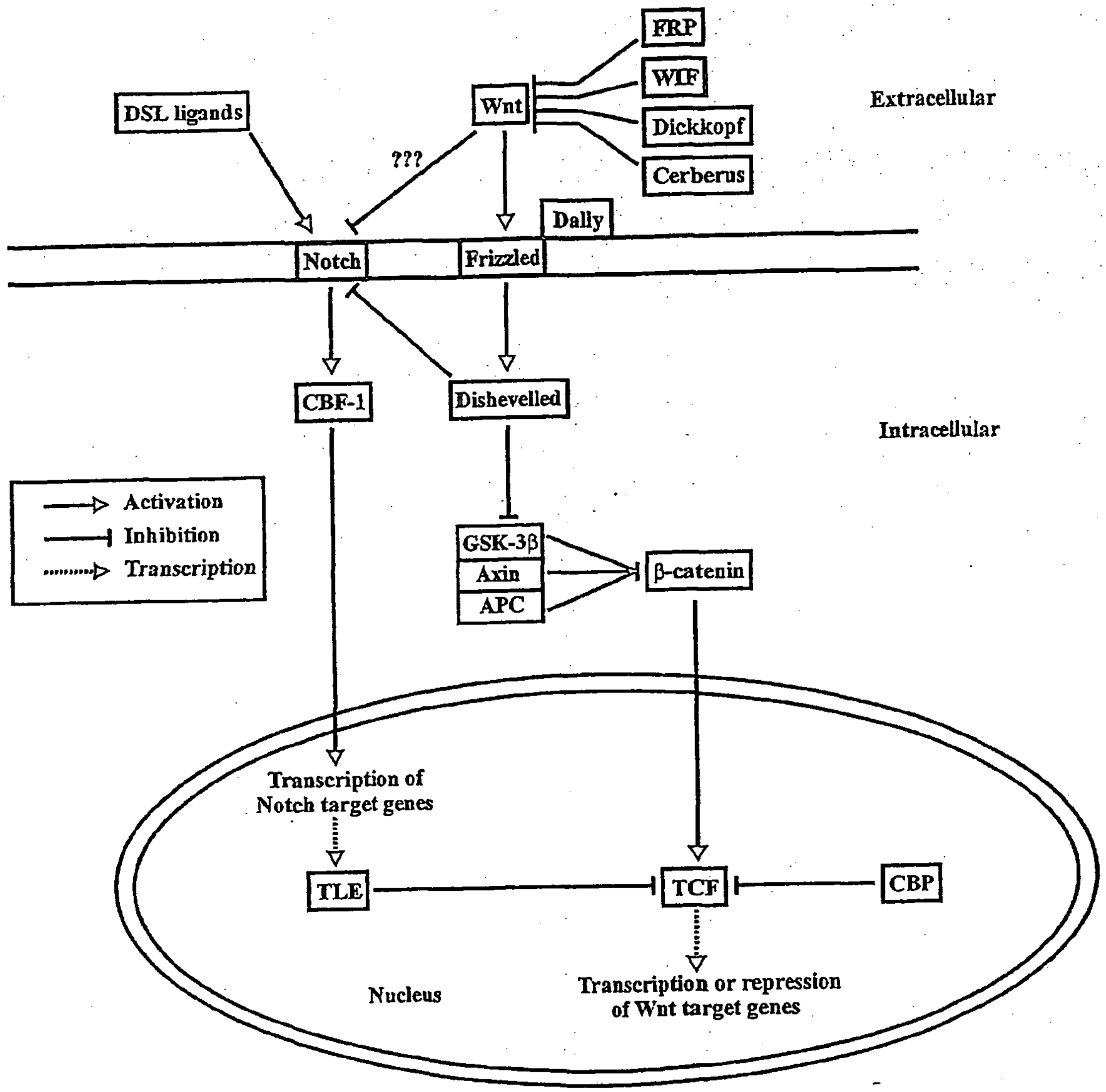
Fig 23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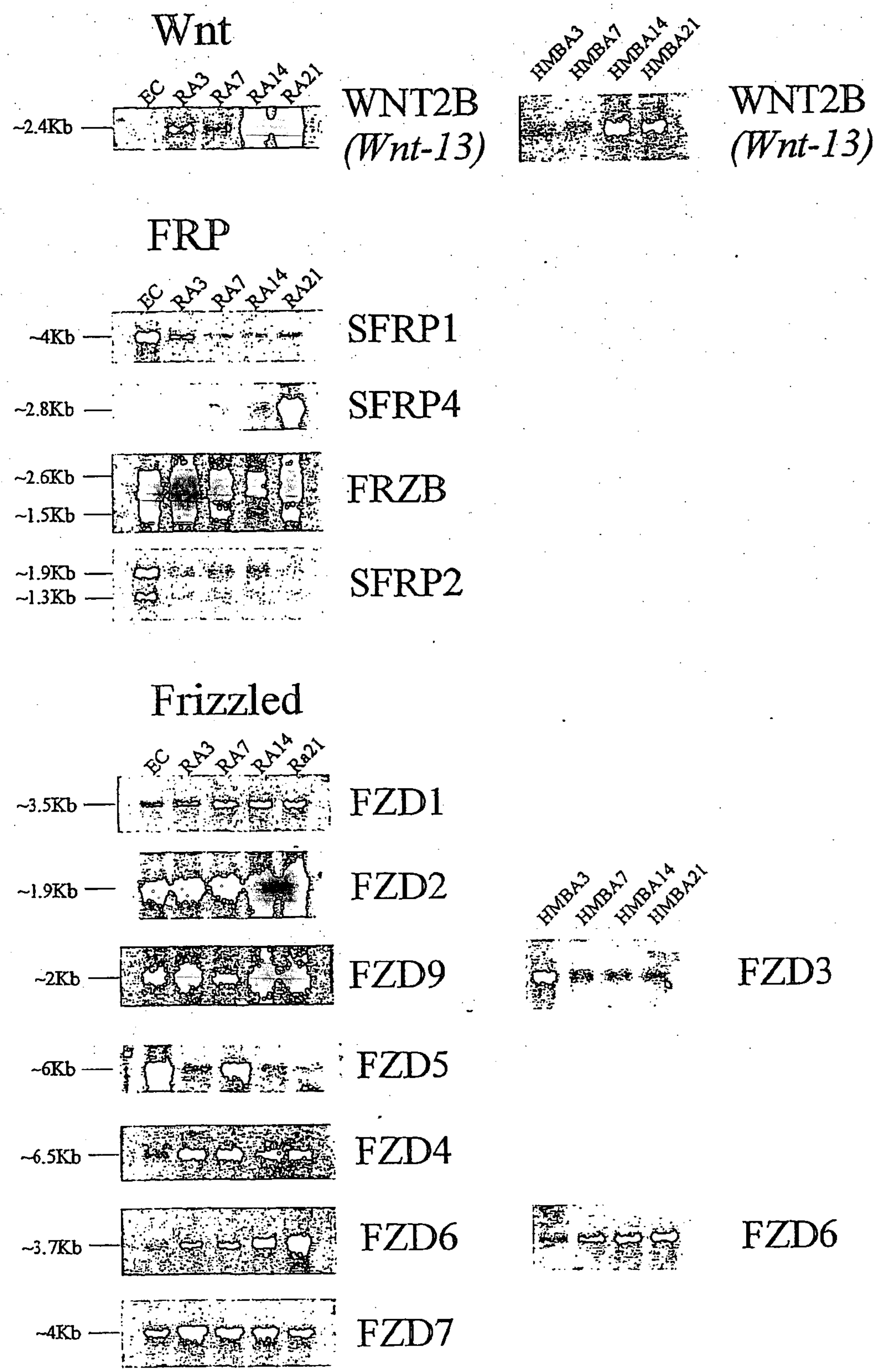
Dickkopf
Cerberus
Wnt
DSL ligands
Extracellular
???
Dally
Notch
Frizzled
CBF-1
Dishevelled
Intracellular
Activation
Inhibition
Transcription
GSK-3β
Axin
APC
β-catenin
Transcription of
Notch target genes
TLE
TCF
CBP
Nucleus
Transcription or repression
of Wnt target genes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(Wnt-13)
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FRP
EC RA3 RA7 RA14 RA21
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FRZB
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SFRP2
Frizzled
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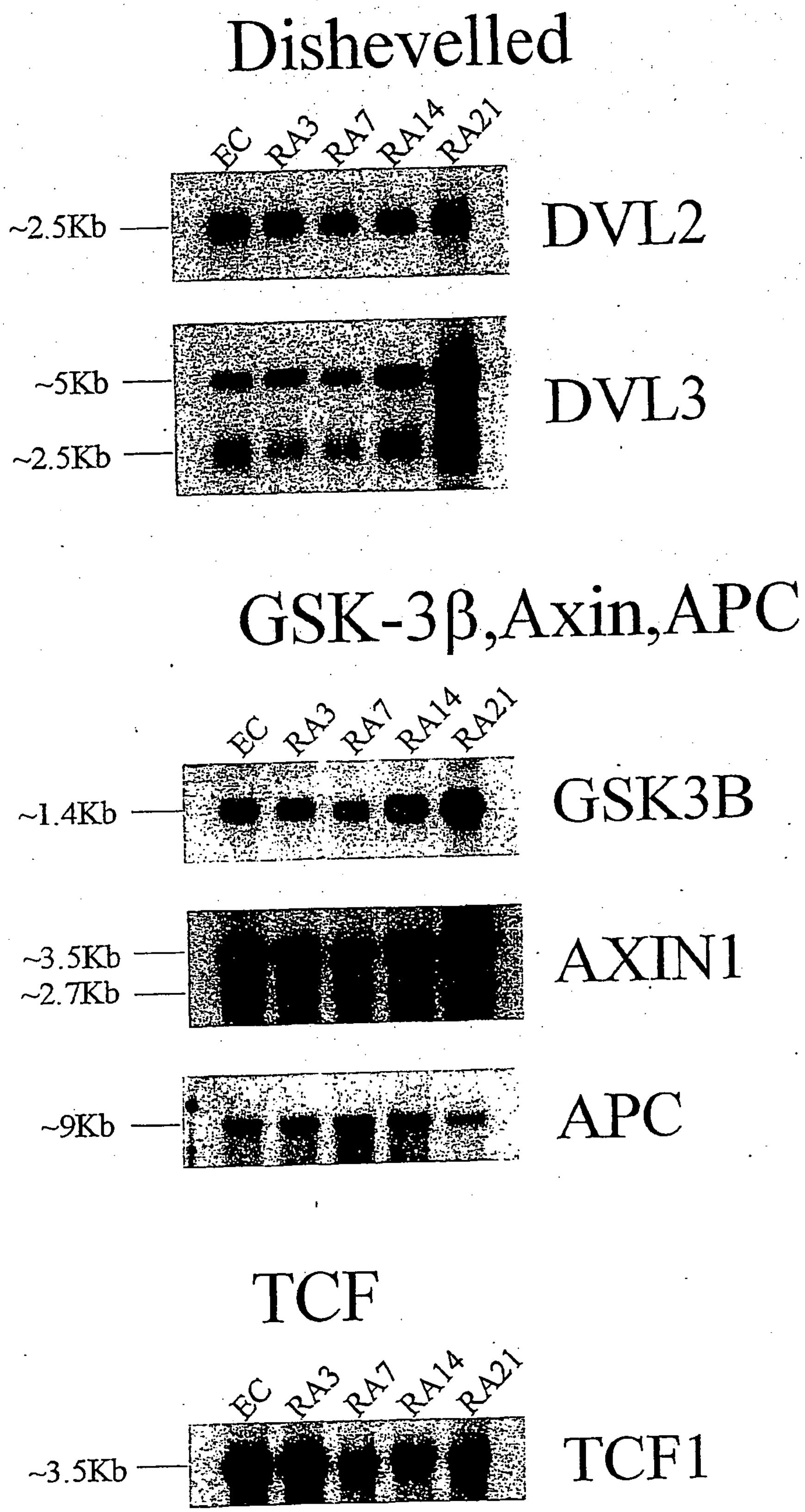
FZD7

Figure 24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AXIN1
~9Kb
APC
TCF
EC
RA3
RA7
RA14
RA21
~3.5Kb
TCF1

Figure 25

Figure 26

ACCGCAGGGGGCTCCCGGACCCTGACTCTGCAGCCGAACCGGCACGGTTTCGTGGGGA
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Figure 27

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AAATACTTTTTTTCAAAATTTTAGTTTTACCTGTAATTAATAAGAACTGATACAAGAC
AAAAACAGTTCCTTCAGATTCTACGGAATGACAGTATATCTCTCTTTATCCTATGTGAT
TCCTGCTCTGAATGCATTATATTTTCCAAACTATACCCATAAATTGTGACTAGTAAAAT
ACTTACACAGAGCAGAATTTTCACAGATGGCAAAAAAATTTAAAGATGTCCAATATAT
GTGGGAAAAGAGCTAACAGAGAGATCATTATTTCTTAAAGATTGGCCATAACCTGTAT
TTTGATAGAATTAGATTGGTAAATACATGTATTCATACATACTCTGTGGTAATAGAGAC
TTGAGCTGGATCTGTACTGCACTGGAGTAAGCAAGAAAATTGGGAAAACTTTTTCGTTT
GTTCAGGTTTTGGCAACACATAGATCATATGTCTGAGGCACAAGTTGGCTGTTCATCTT
TGAAACCAGGGGATGCACAGTCTAAATGAATATCTGCATGGGATTTGCTATCATAATA
TTTACTATGCAGATGAATTCAGTGTGAGGTCCTGTGTCCGTACTATCCTCAAATTATTTA
[illegible]CAGGAGGTTTCACAAAATGGACT

CCTGAAGTAGACAGAGTAGTGAGGTTTCATTGCCCTCTATAAGCTTCTGACTAGCCAAT
GGCATCATCCAATTTTCTTCCCAAACCTCTGCAGCATCTGCTTTATTGCCAAAGGGCTA
GTTTCGGTTTTCTGCAGCCATTGCGGTTAAAAAATATAAGTAGGATAACTTGTAAAACC
TGCATATTGCTAATCTATAGACACCACAGTTTCTAAATTCTTTGAAACCACTTTACTACT
TTTTTAAACTTAACTCAGTTCTAAATACTTTGTCTGGAGCACAAAACAATAAAAGGTT
ATCTTATAGTCGTGACTTTAAACTTTTGTAGACCACAATTCACTTTTTAGTTTTCTTTTA
CTTAAATCCCATCTGCAGTCTCAAATTTAAGTTCTCCCAGTAGAGATTGAGTTTGAGCC
TGTATATCTATTAAAAATTTCAACTTCCCACATATATTTACTAAGATGATTAAGACTTA
CATTTTCTGCACAGGTCTGCAAAAACAAAAATTATAAACTAGTCCATCCAAGAACCAA
AGTTTGTATAAACAGGTTGCTATAAGCTTGGTGAAATGAAAATGGAACATTTCAATCA
AACATTTCCTATATAACAATTATTATATTTACAATTTGGTTTCTGCAATATTTTTCTTAT
GTCCACCCTTTTAAAAATTATTATTTGAAGTAATTTATTTACAGGAAATGTTAATGAGA
TGTATTTTCTTATAGAGATATTTCTTACAGAAAGCTTTGTAGCAGAATATATTTGCAGCT
ATTGACTTTGTAATTTAGGAAAAATGTATAATAAGATAAAATCTATTAAATTTTTCTCC
TCTAAAAACTGAATTCAAAGC

Figure 28

ACACACAGGCGGCGGCTGCGGGCGCAGAGCGGAGATGCAGCGGCTTGGGGCCACCCT
GCTGTGCCTGCTGCTGGCGGCGGCGGTCCCCACGGCCCCCGCGCCCGCTCCGACGGCG
ACCTCGGCTCCAGTCAAGCCCGGCCCGGCTCTCAGCTACCCGCAGGAGGAGGCCACCC
TCAATGAGATGTTCCGCGAGGTTGAGGAACTGATGGAGGACACGCAGCACAAATTGCG
CAGCGCGGTGGAAGAGATGGAGGCAGAAGAAGCTGCTGCTAAAGCATCATCAGAAGT
GAACCTGGCAAACTTACCTCCCAGCTATCACAATGAGACCAACACAGACACGAAGGTT
GGAAATAATACCATCCATGTGCACCGAGAAATTCACAAGATAACCAACAACCAGACTG
GACAAATGGTCTTTTCAGAGACAGTTATCACATCTGTGGGAGACGAAGAAGGCAGAAG
GAGCCACGAGTGCATCATCGACGAGGACTGTGGGCCCAGCATGTACTGCCAGTTTGCC
AGCTTCCAGTACACCTGCCAGCCATGCCGGGGCCAGAGGATGCTCTGCACCCGGGACA
GTGAGTGCTGTGGAGACCAGCTGTGTGTCTGGGGTCACTGCACCAAAATGGCCACCAG
GGGCAGCAATGGGACCATCTGTGACAACCAGAGGGACTGCCAGCCGGGGCTGTGCTGT
GCCTTCCAGAGAGGCCTGCTGTTCCCTGTGTGCACACCCCTGCCCGTGGAGGGCGAGCT
TTGCCATGACCCCGCCAGCCGGCTTCTGGACCTCATCACCTGGGAGCTAGAGCCTGATG
GAGCCTTGGACCGATGCCCTTGTGCCAGTGGCCTCCTCTGCCAGCCCCACAGCCACAGC
CTGGTGTATGTGTGCAAGCCGACCTTCGTGGGGAGCCGTGACCAAGATGGGGAGATCC
TGCTGCCCAGAGAGGTCCCCGATGAGTATGAAGTTGGCAGCTTCATGGAGGAGGTGCG
CCAGGAGCTGGAGGACCTGGAGAGGAGCCTGACTGAAGAGATGGCGCTGGGGGAGCC
TGCGGCTGCCGCCGCTGCACTGCTGGGAGGGGAAGAGATTTAGATCTGGACCAGGCTG
TGGGTAGATGTGCAATAGAAATAGCTAATTTATTTCCCCAGGTGTGTGCTTTAGGCGTG
GGCTGACCAGGCTTCTTCCTACATCTTCTTCCCAGTAAGTTTCCCCTCTGGCTTGACAGC
ATGAGGTGTTGTGCATTTGTTCAGCTCCCCCAGGCTGTTCTCCAGGCTTCACAGTCTGG
TGCTTGGGAGAGTCAGGCAGGGTTAAACTGCAGGAGCAGTTTGCCACCCCTGTCCAGA
TTATTGGCTGCTTTGCCTCTACCAGTTGGCAGACAGCCGTTTGTTCTACATGGCTTTGAT
AATTGTTTGAGGGGAGGAGATGGAAACAATGTGGAGTCTCCCTCTGATTGGTTTTGGG
GAAATGTGGAGAAGAGTGCCCTGCTTTGCAAACATCAACCTGGCAAAAATGCAACAAA
TGAATTTTCCACGCAGTTCTTTCCATGGGCATAGGTAAGCTGTGCCTTCAGCTGTTGCA
GATGAAATGTTCTGTTCACCCTGCATTACATGTGTTTATTCATCCAGCAGTGTTGCTCAG

CTCCTACCTCTGTGCCAGGGCAGCATTTTCATATCCAAGATCAATTCCCTCTCTCAGCA
CAGCCTGGGGAGGGGGTCATTGTTCTCCTCGTCCATCAGGGATCTCAGAGGCTCAGAG
ACTGCAAGCTGCTTGCCCAAGTCACACAGCTAGTGAAGACCAGAGCAGTTTCATCTGG
TTGTGACTCTAAGCTCAGTGCTCTCTCCACTACCCCACACCAGCCTTGGTGCCACCAAA
AGTGCTCCCCAAAAGGAAGGAGAATGGGATTTTTCTTTTGAGGCATGCACATCTGGAA
TTAAGGTCAAACTAATTCTCACATCCCTCTAAAAGTAAACTACTGTTAGGAACAGCAGT
GTTCTCACAGTGTGGGGCAGCCGTCCTTCTAATGAAGACAATGATATTGACACTGTCCC
TCTTTGGCAGTTGCATTAGTAACTTTGAAAGGTATATGACTGAGCGTAGCATACAGGTT
AACCTGCAGAAACAGTACTTAGGTAATTGTAGGGCGAGGATTATAAATGAAATTTGCA
AAATCACTTAGCAGCAACTGAAGACAATTATCAACCACGTGGAGAAAATCAAACCGAG
CAGGGCTGTGTGAAACATGGTTGTAATATGCGACTGCGAACACTGAACTCTACGCCAC
TCCACAAATGATGTTTTCAGGTGTCATGGACTGTTGCCACCATGTATTCATCCAGAGTT
CTTAAAGTTTAAAGTTGCACATGATTGTATAAGCATGCTTTCTTTGAGTTTTAAATTATG
TATAAACATAAGTTGCATTTAGAAATCAAGCATAAATCACTTCAACTGCTCTTCT

Figure 29

GACAAACAGACGACGTGCTGAGCTGCCAGCTTAGTGGAAGCTCTGCTCTGGGTGGAGA
GCAGCCTCGCTTTGGTGACGCACAGTGCTGGGACCCTCCAGGAGCCCCGGGATTGAAG
GATGGTGGCGGCCGTCCTGCTGGGGCTGAGCTGGCTCTGCTCTCCCCTGGGAGCTCTGG
TCCTGGACTTCAACAACATCAGGAGCTCTGCTGACCTGCATGGGGCCCGGAAGGGCTC
ACAGTGCCTGTCTGACACGGACTGCAATACCAGAAAGTTCTGCCTCCAGCCCCGCGAT
GAGAAGCCGTTCTGTGCTACATGTCGTGGGTTGCGGAGGAGGTGCCAGCGAGATGCCA
TGTGCTGCCCTGGGACACTCTGTGTGAACGATGTTTGTACTACGATGGAAGATGCAACC
CCAATATTAGAAAGGCAGCTTGATGAGCAAGATGGCACACATGCAGAAGGAACAACT
GGGCACCCAGTCCAGGAAAACCAACCCAAAAGGAAGCCAAGTATTAAGAAATCACAA
GGCAGGAAGGGACAAGAGGGAGAAAGTTGTCTGAGAACTTTTGACTGTGGCCCTGGAC
TTTGCTGTGCTCGTCATTTTTGGACGAAAATTTGTAAGCCAGTCCTTTTGGAGGGACAG
GTCTGCTCCAGAAGAGGGCATAAAGACACTGCTCAAGCTCCAGAAATCTTCCAGCGTT
GCGACTGTGGCCCTGGACTACTGTGTCGAAGCCAATTGACCAGCAATCGGCAGCATGC
TCGATTAAGAGTATGCCAAAAAATAGAAAAGCTATAAATATTTCAAAATAAAGAAGAA
TCCACATTGCATTTGAG

Figure 30

ATGGGGCTCTGGGCGCTGTTGCCTGGCTGGGTTTCTGCTACGCTGCTGCTGGCGCTGGC
CGCTCTGCCCGCAGCCCTGGCTGCCAACAGCAGTGGCCGATGGTGGGGTATTGTGAAC
GTAGCCTCCTCCACGAACCTGCTTACAGACTCCAAGAGTCTGCAACTGGTACTCGAGCC
CAGTCTGCAGCTGTTGAGCCGCAAACAGCGGCGCCTGATACGCCAAAATCCGGGGATC
CTGCACAGCGTGAGTGGGGGGCTGCAGAGTGCCGTGCGCGAGTGCAAGTGGCAGTTCC
GGAATCGCCGCTGGAACTGTCCCACTGCTCCAGGGCCCCACCTCTTCGGCAAGATCGTC
AACCGAGGCTGTCGAGAAACGGCGTTTATCTTCGCTATCACCTCCGCCGGGGTCACCC
ATTCGGTGGCGCGCTCCTGCTCAGAAGGTTCCATCGAATCCTGCACGTGTGACTACCGG
CGGCGCGGCCCCGGGGGCCCCGACTGGCACTGGGGGGGCTGCAGCGACAACATTGACT
TCGGCCGCCTCTTCGGCCGGGAGTTCGTGGACTCCGGGGAGAAGGGGCGGGACCTGCG
CTTCCTCATGAACCTTCACAACAACGAGGCAGGCCGTACGACCGTATTCTCCGAGATG
CGCCAGGAGTGCAAGTGCCACGGGATGTCCGGCTCATGCACGGTGCGCACGTGCTGGA
TCGGCCTGCCCACGCTGCGCGCCGTGGGCGATGTGCTGCGCGACCGCTTCGACGGCGC

CTCGCGCGTCCTGTACGGCAACCGCGGCAGCAACCGCGCTTCGCGAGCGGAGCTGCTG
CGCCTGGAGCCGGAAGACCCGGCCCACAAACCGCCCTCCCCCACGACCTCGTCTACT
TCGAGAAATCGCCCAACTTCTGCACGTACAGCGGACGCCTGGGCACAGCAGGCACGGC
AGGGCGCGCCTGTAACAGCTCGTCGCCCGCGCTGGACGGCTGCGAGCTGCTCTGCTGC
GGCAGGGGCCACCGCACGCGCACGCAGCGCGTCACCGAGCGCTGCAACTGCACCTTCC
ACTGGTGCTGCCACGTCAGCTGCCGCAACTGCACGCACACGCGCGTACTGCACGAGTG
TCTGTGA

Figure 31

MGLWALLPGWVSATLLLALAALPAALAANSSGRWWGIVNVASSTNLLTDSKSLQLVLEPS
LQLLSRKQRRLIRQNPGILHSVSGGLQSAVRECKWQFRNRRWNCPTAPGPHLFGKIVNRGC
RETAFIFAITSAGVTHSVARSCSEGSIESCTCDYRRRGPGGPDWHWGGCSDNIDFGRLFGRE
FVDSGEKGRDLRFLMNLHNNEAGRTTVFSEMRQECKCHGMSGSCTVRTCWMRLPTLRAV
GDVLRDRFDGASRVLYGNRGSNRASRAELLRLEPEDPAHKPPSPHDLVYFEKSPNFCTYSG
RLGTAGTAGRACNSSSPALDGCELLCCGRGHRTRTQRVTERCNCTFHWCCHVSCRNCTHT
RVLHECL

Figure 32

AGCAGAGCGGACGGGCGCGCGGGAGGCGCGCAGAGCTTTCGGGCTGCAGGCGCTCGC
TGCCGCTGGGGAATTGGGCTGTGGGCGAGGCGGTCCGGGCTGGCCTTTATCGCTCGCT
GGGCCCATCGTTTGAAACTTTATCAGCGAGTCGCCACTCGTCGCAGGACCGAGCGGGG
GGCGGGGGCGCGGCGAGGCGGCGGCCGTGACGAGGCGCTCCCGGAGCTGAGCGCTTC
TGCTCTGGGCACGCATGGCGCCCGCACACGGAGTCTGACCTGATGCAGACGCAAGGGG
GTTAATATGAACGCCCCTCTCGGTGGAATCTGGCTCTGGCTCCCTCTGCTCTTGACCTG
GCTCACCCCCGAGGTCAACTCTTCATGGTGGTACATGAGAGCTACAGGTGGCTCCTCCA
GGGTGATGTGCGATAATGTGCCAGGCCTGGTGAGCAGCCAGCGGCAGCTGTGTCACCG
ACATCCAGATGTGATGCGTGCCATTAGCCAGGGCGTGGCCGAGTGGACAGCAGAATGC
CAGCACCAGTTCCGCCAGCACCGCTGGAATTGCAACACCCTGGACAGGGATCACAGCC
TTTTTGGCAGGGTCCTACTCCGAAGTAGTCGGGAATCTGCCTTTGTTTATGCCATCTCCT
CAGCTGGAGTTGTATTTGCCATCACCAGGGCCTGTAGCCAAGGAGAAGTAAAATCCTG
TTCCTGTGATCCAAAGAAGATGGGAAGCGCCAAGGACAGCAAAGGCATTTTTGATTGG
GGTGGCTGCAGTGATAACATTGACTATGGGATCAAATTTGCCCGCGCATTTGTGGATGC
AAAGGAAAGGAAAGGAAAGGATGCCAGAGCCCTGATGAATCTTCACAACAACAGAGC
TGGCAGGAAGGCTGTAAAGCGGTTCTTGAAACAAGAGTGCAAGTGCCACGGGGTGAG
CGGCTCATGTACTCTCAGGACATGCTGGCTGGCCATGGCCGACTTCAGGAAAACGGGC
GATTATCTCTGGAGGAAGTACAATGGGGCCATCCAGGTGGTCATGAACCAGGATGGCA
CAGGTTTCACTGTGGCTAACGAGAGGTTTAAGAAGCCAACGAAAAATGACCTCGTGTA
TTTTGAGAATTCTCCAGACTACTGTATCAGGGACCGAGAGGCAGGCTCCCTGGGTACA
GCAGGCCGTGTGTGCAACCTGACTTCCCGGGGCATGGACAGCTGTGAAGTCATGTGCT
GTGGGAGAGGCTACGACACCTCCCATGTCACCCGGATGACCAAGTGTGGGTGTAAGTT
CCACTGGTGCTGCGCCGTGCGCTGTCAGGACTGCCTGGAAGCTCTGGATGTGCACACA
TGCAAGGCCCCCAAGAACGCTGACTGGACAACCGCTACATGACCCCAGCAGGCGTCAC
CATCCACCTTCCCTTCTACAAGGACTCCATTGGATCTGCAAGAACACTGGACCTTTGGG
TTCTTTCTGGGGGGATATTTCCTAAGGCATGTGGCCTTTATCTCAACGGAAGCCCCCTC
TTGCTGCCTGGCGGCGGCAGCATGGGGGCCACACGCTGCACCTAAAGCCTACCCTAT

TCTATCCATCTCCTGGTGTTCTGCAGTCATCTCCCCTCCTGGCGAGTTCTCTTTGGAAAT
AGCATGACAGGCTGTTCAGCCGGGAGGGTGGTGGGCCCAGACCACTGTCTCCACCCAC
CTTGACGTTTCTTCTTTCTAGAGCAGTTGGCCAAGCAGAAAAAAAGTGTCTCAAAGG
AGCTTTCTCAATGTCTTCCCACAAATGGTCCCAATTAAGAAATTCCATACTTCTCTCAG
ATGGAACAGTAAAGAAAGCAGAATCAACTGCCCCTGACTTAACTTTAACTTTTGAAAA
GACCAAGACTTTTGTCTGTACAAGTGGTTTTACAGCTACCACCCTTAGGGTAATTGGTA
ATTACCTGGAGAAGAATGGCTTTCAATACCCTTTTAAGTTTAAAATGTGTATTTTTCAA
GGCATTTATTGCCATATTAAAATCTGATGTAACAAGGTGGGGACGTGTGTCCTTTGGTA
CTATGGTGTGTTGTATCTTTGTAAGAGCAAAAGCCTCAGAAAGGGATTGCTTTGCATTA
CTGTCCCCTTGATATAAAAAATCTTTAGGGAATGAGAGTTCCTTCTCACTTAGAATCTG
AAGGGAATTAAAAAGAAGATGAATGGTCTGGCAATATTCTGTAACTATTGGGTGAATA
TGGTGGAAAATAATTTAGTGGATGGAATATCAGAAGTATATCTGTACAGATCAAGAAA
AAAAGGAAGAATAAAATTCCTATATCAT

Figure 33

MNAPLGGIWLWLPLLLTWLTPEVNSSWWYMRATGGSSRVMCDNVPGLVSSQRQLCHRH
PDVMRAISQGVAEWTAECQHQFRQHRWNCNTLDRDHSLFGRVLLRSSRESAFVYAISSAG
VVFAITRACSQGEVKSCSCDPKKMGSAKDSKGIFDWGGCSDNIDYGIKFARAFVDAKERK
GKDARALMNLHNNRAGRKAVKRFLKQECKCHGVSGSCTLRTCWLAMADFRKTGDYLW
RKYNGAIQVVMNQDGTGFTVANERFKKPTKNDLVYFENSPDYCIRDREAGSLGTAGRVC
NLTSRGMDSCEVMCCGRGYDTSHVTRMTKCGCKFHWCCAVRCQDCLEALDVHTCKAPK
NADWTTAT

Figure 34

CGGGAGTCTTCGGGGAGCTATGCTGAGACCGGGTGGTGCGGAGGAAGCTGCGCAGCTC
CCGCTTCGGCGCGCCAGCGCCCCGGTCCCTGTGCCGTCGCCCGCGGCCCCCGACGGCTC
CCGGGCTTCGGCCCGCCTAGGTCTTGCCTGCCTTCTGCTCCTGCTGCTGCTGACGCTGC
CGGCCCGCGTAGACACGTCCTGGTGGTACATTGGGGCACTGGGGGCACGAGTGATCTG
TGACAATATCCCTGGTTTGGTGAGCCGGCAGCGGCAGCTGTGCCAGCGTTACCCAGAC
ATCATGCGTTCAGTGGGCGAGGGTGCCCGAGAATGGATCCGAGAGTGTCAGCACCAAT
TCCGCCACCACCGCTGGAACTGTACCACCCTGGACCGGGACCACACCGTCTTTGGCCGT
GTCATGCTCAGAAGTAGCCGAGAGGCAGCTTTTGTATATGCCATCTCATCAGCAGGGG
TAGTCCACGCTATTACTCGCGCCTGTAGCCAGGGTGAACTGAGTGTGTGCAGCTGTGAC
CCCTACACCCGTGGCCGACACCATGACCAGCGTGGGGACTTTGACTGGGGTGGCTGCA
GTGACAACATCCACTACGGTGTCCGTTTTGCCAAGGCCTTCGTGGATGCCAAGGAGAA
GAGGCTTAAGGATGCCCGGGCCCTCATGAACTTACATAATAACCGCTGTGGTCGCACG
GCTGTGCGGCGGTTTCTGAAGCTGGAGTGTAAGTGCCATGGCGTGAGTGGTTCCTGTAC
TCTGCGCACCTGCTGGCGTGCACTCTCAGATTTCCGCCGCACAGGTGATTACCTGCGGC
GACGCTATGATGGGGCTGTGCAGGTGATGGCCACCCAAGATGGTGCCAACTTCACCGC
AGCCCGCCAAGGCTATCGCCGTGCCACCCGGACTGATCTTGTCTACTTTGACAACTCTC
CAGATTACTGTGTCTTGGACAAGGCTGCAGGTTCCCTAGGCACTGCAGGCCGTGTCTGC
AGCAAGACATCAAAAGGAACAGACGGTTGTGAAATCATGTGCTGTGGCCGAGGGTAC
GACACAACTCGAGTCACCCGTGTTACCCAGTGTGAGTGCAAATTCCACTGGTGCTGTGC
TGTACGGTGCAAGGAATGCAGAAATACTGTGGACGTCCATACTTGCAAAGCCCCCAAG
AAGGCAGAGTGGCTGGACCAGACCTGAACACACAGATACCTCACTCATCCCTCCAATT
CAAGCCTCTCAACTCAAAAGCACAAGATCCTTGCATGCACACCTTCCTCCACCCTCCAC
CCTGGGCTGCTACCGCTTCTATTTAAGGATGTAGAGAGTAATCCATAGGGACCATGGTG
TCCTGGCTGGTTCCTTAGCCCTGGGAAGGAGTTGTCAGGGGATATAAGAAACTGTGCA
AGCTCCCTGATTTCCCGCTCTGGAGATTTGAAGGGAGAGTAGAAGAGATAGGGGGTCT
[illegible]TGAAATGACTTGGACTAAACTACGTAGTTGAGGCTCCTTTTTTCTTTCCTTTGC

ACCAGCTTCCCGACACTTCTTGGTGTGCAAGAGGAAGGGTACCTGTAGAGAGCTTCTTT
TTGTTTCTACCTGGCCAAAGTTAGATGGGACAAAGATGAATGGCATGTCCCTTCTCTGA
AGTCCGTTTGAGCAGAACTACCTGGTACCCCGAAAGAAAAATCTTAGGCTACCACATT
CTATTATTGAGAGCCTGAGATGTTAGCCATAGTGGACAAGGTTCCATTCACATGCTCAT
ATGTTTATAAACTGTGTTTTGTAGAAGAAAAAGAATCATAACAATACAAACACACATT
CATTCTCTCTTTTTCTCTCTACCATTCTCAACCTGTATTGGACAGCACTGCCTCTTTTGCT
TACTTGCTGCCTGTTCAAACTGAGGTGGAATGCAGTGGTTCCCATGCTTAACAGATCAT
TAAAACACCCTAGAACACTCCTAGGATAGATTAATGT

Figure 35

MLDGLGVVAISIFGIQLKTEGSLRTAVPGIPTQSAFNKCLQRYIGALGARVICDNIPGLVSRQ
RQLCQRYPDIMRSVGEGAREWIRECQHQFRHHRWNCTTLDRDHTVFGRVMLRSSREAAF
VYAISSAGVIHAITRACSQGELSVCSCDPYTRGRHHDQRGTFDWGGCSDNIHYGVRFAKAF
VDAKEKRLKDARALMNLHNNRCGRTAVRRFVKLECKCHGVSGSCTLRTCWRALSDFRRT
GDYLRRRYDGAVQVMATQDGANFTAARQGYRRATRSDLVYFDNSPDYCVLDKAAGSLG
TAGRVCSKTSKGTDGCEIMCCGRGYDTTRVTRVTQCECKFHWCCAVRCKECRNTVDVHT
CKAPKKAEWLDQT

Figure 36

GCGCTTCTGACAAGCCCGAAAGTCATTTCCAATCTCAAGTGGACTTTGTTCCAACTATT
GGGGGCGTCGCTCCCCCTCYTCATGGTCGCGGCAAACTTCCTCCTCGGCGCCTCTTCT
AATGGAGCCCCACCTGCTCGGGCTGCTCCTCGGCCTCCTGCTCGGTGGCACCAGGGTCC
TCGCTGGCTACCCAATTTGGTGGTCCCTGGCCCTGGGCCAGCAGTACACATCTCTGGGC
TCACAGCCCCTGCTCTGCGGCTCCATCCCAGGCCTGGTCCCCAAGCAACTGCGCTTCTG
CCGCAATTACATCGAGATCATGCCCAGCGTGGCCGAGGGCGTGAAGCTGGGCATCCAG
GAGTGCCAGCACCAGTTCCGGGGCCGCCGCTGGAACTGCACCACCATAGATGACAGCC
TGGCCATCTTTGGGCCCGTCCTCGACAAAGCCACCCGCGAGTCGGCCTTCGTTCACGCC
ATCGCCTCGGCCGGCGTGGCCTTCGCCGTCACCCGCTCCTGCGCCGAGGGCACCTCCAC
CATTTGCGGCTGTGACTCGCATCATAAGGGGCCGCCTGGCGAAGGCTGGAAGTGGGGC
GGCTGCAGCGAGGACGCTGACTTCGGCGTGTTAGTGTCCAGGGAGTTCGCGGATGCGC
GCGAGAACAGGCCGGACGCGCGCTCGGCCATGAACAAGCACAACAACGAGGCGGGCC
GCACGACTATCCTGGACCACATGCACCTCAAATGCAAGTGCCACGGGCTGTCGGGCAG
CTGTGAGGTGAAGACCTGCTGGTGGGCGCAGCCTGACTTCCGTGCCATCGGTGACTTCC
TCAAGGACAAGTATGACAGCGCCTCGGAGATGGTAGTAGAGAAGCACCGTGAGTCCCG
AGGCTGGGTGGAGACCCTCCGGGCCAAGTACTCGCTCTTCAAGCCACCCACGGAGAGG
GACCTGGTCTACTACGAGAACTCCCCCAACTTTTGTGAGCCCAACCCAGAGACGGGTT
CCTTTGGCACAAGGGACCGGACTTGCAATGTCACCTCCCACGGCATCGATGGCTGCGA
TCTGCTCTGCTGTGGCCGGGGCCACAACACGAGGACGGAGAAGCGGAAGGAAAAATG
CCACTGCATCTTCCACTGGTGCTGCTACGTCAGCTGCCAGGAGTGTATTCGCATCTACG
ACGTGCACACCTGCAAGTAGGGCACCAG

MEPHLLGLLLGLLLGGTRVLAGYPIWWSLALGQQYTSLGSQPLLCGSIPGLVPKQLRFCRN
YIEIMPSVAEGVKLGIQECQHQFRGRRWNCTTIDDSLAIFGPVLDKATRESAFVHAIASAGV
AFAVTRSCAEGTSTICGCDSHHKGPPGEGWKWGGCSEDADFGVLVSREFADARENRPDAR
SAMNKHNNEAGRTTILDHMHLKCKCHGLSGSCEVKTCWWAQPDFRAIGDFLKDKYDSAS
EMVVEKHRESRGWVETLRAKYSLFKPPTERDLVYYENSPNFCEPNPETGSFGTRDRTCNVT
SHGIDGCDLLCCGRGHNTRTEKRKEKCHCI

Figure 38

ATGAGTCCCCGCTCGTGCCTGCGTTCGCTGCGCCTCCTCGTCTTCGCCGTCTTCTCAGCC
GCCGCGAGCAACTGGCTGTACCTGGCCAAGCTGTCGTCGGTGGGGAGCATCTCAGAGG
AGGAGACGTGCGAGAAACTCAAGGGCCTGATCCAGAGGCAGGTGCAGATGTGCAAGC
GGAACCTGGAAGTCATGGACTCGGTGCGCCGCGGTGCCCAGCTGGCCATTGAGGAGTG
CCAGTACCAGTTCCGGAACCGGCGCTGGAACTGCTCCACACTCGACTCCTTGCCCGTCT
TCGGCAAGGTGGTGACGCAAGGGATTCGGGAGGCGGCCTTGGTGTACGCCATCTCTTC
GGCAGGTGTGGCCTTTGCAGTGACGCGGGCGTGCAGCAGTGGGGAGCTGGAGAAGTGC
GGCTGTGACAGGACAGTGCATGGGGTCAGCCCACAGGGCTTCCAGTGGTCAGGATGCT
CTGACAACATCGCCTACGGTGTGGCCTTCTCACAGTCGTTTGTGGATGTGCGGGAGAGA
AGCAAGGGGGCCTCGTCCAGCAGAGCCCTCATGAACCTCCACAACAATGAGGCCGGCA
GGAAGGCCATCCTGACACACATGCGGGTGGAATGCAAGTGCCACGGGGTGTCAGGCTC
CTGTGAGGTAAAGACGTGCTGGCGAGCCGTGCCGCCCTTCCGCCAGGTGGGTCACGCA
CTGAAGGAGAAGTTTGATGGTGCCACTGAGGTGGAGCCACGCCGCGTGGGCTCCTCCA
GGGCACTGGTGCCACGCAACGCACAGTTCAAGCCGCACACAGATGAGGACTTGGTGTA
CTTGGAGCCTAGCCCCGACTTCTGTGAGCAGGACATGCGCAGCGGCGTGCTGGGCACG
AGGGGCCGCACATGCAACAAGACGTCCAAGGCCATCGACGGCTGTGAGCTGCTGTGCT
GTGGCCGCGGCTTCCACACGGCGCAGGTGGAGCTGGCTGAACGCTGCAGCTGCAAATT
CCACTGGTGCTGCTTCGTCAAGTGCCGGCAGTGCCAGCGGCTCGTGGAGTTGCACACG
TGCCGATGA

Figure39

MSPRSCLRSLRLLVFAVFSAAASNWLYLAKLSSVGSISEEETCEKLKGLIQRQVQMCKRNL
EVMDSVRRGAQLAIEECQYQFRNRRWNCSTLDSLPVFGKVVTQGIREAALVYAISSAGVA
FAVTRACSSGELEKCGCDRTVHGVSPQGFQWSGCSDNIAYGVAFSQSFVDVRERSKGASSS
RALMNLHNNEAGRKAILTHMRVECKCHGVSGSCEVKTCWRAVPPFRQVGHALKEKFDG
ATEVEPRRVGSSRALVPRNAQFKPHTDEDLVYLEPSPDFCEQDMRSGVLGTRGRTCNKTS
KAIDGCELLCCGRGFHTAQVELAERCSCKFHWCCFVKCRQCQRLVELHTCR

Figure 40

ATTAATTCTGGCTCCACTTGTTGCTCGGCCCAGGTTGGGGAGAGGACGGAGGGTGGCC
GCAGCGGGTTCCTGAGTGAATTACCCAGGAGGGACTGAGCACAGCACCAACTAGAGA
GGGGTCAGGGGGTGCGGGACTCGAGCGAGCAGGAAGGAGGCAGCGCCTGGCACCAGG
GCTTTGACTCAACAGAATTGAGACACGTTTGTAATCGCTGGCGTGCCCCGCGCACAGG
ATCCCAGCGAAAATCAGATTTCCTGGTGAGGTTGCGTGGGTGGATTAATTTGGAAAAA
GAAACTGCCTATATCTTGCCATCAAAAAACTCACGGAGGAGAAGCGCAGTCAATCAAC
AGTAAACTTAAGAGACCCCCGATGCTCCCCTGGTTTAACTTGTATGCTTGAAAATTATC
TGAGAGGGAATAAACATCTTTTCCTTCTTCCCTCTCCAGAAGTCCATTGGAATATTAAG
GGGACGCACTTGCTTTGGGGATGGCTGGAAGTGCAATGTCTTCCAAGTTCTTCCTAGTGG

CTTTGGCCATATTTTTCTCCTTCGCCCAGGTTGTAATTGAAGCCAATTCTTGGTGGTCGC
TAGGTATGAATAACCCTGTTCAGATGTCAGAAGTATATATTATAGGAGCACAGCCTCTC
TGCAGCCAACTGGCAGGACTTTCTCAAGGACAGAAGAAACTGTGCCACTTGTATCAGG
ACCACATGCAGTACATCGGAGAAGGCGCGAAGACAGGCATCAAAGAATGCCAGTATC
AATTCCGACATCGACGGTGGAACTGCAGCACTGTGGATAACACCTCTGTTTTTGGCAGG
GTGATGCAGATAGGCAGCCGCGAGACGGCCTTCACATACGCCGTGAGCGCAGCAGGG
GTGGTGAACGCCATGAGCCGGGCGTGCCGCGAGGGCGAGCTGTCCACCTGCGGCTGCA
GCCGCGCCGCGCGCCCCAAGGACCTGCCGCGGGACTGGCTCTGGGGCGGCTGCGGCGA
CAACATCGACTATGGCTACCGCTTTGCCAAGGAGTTCGTGGACGCCCGCGAGCGGGAG
CGCATCCACGCCAAGGGCTCCTACGAGAGTGCTCGCATCCTCATGAACCTGCACAACA
ACGAGGCCGGCCGCAGGACGGTGTACAACCTGGCTGATGTGGCCTGCAAGTGCCATGG
GGTGTCCGGCTCATGTAGCCTGAAGACATGCTGGCTGCAGCTGGCAGACTTCCGCAAG
GTGGGTGATGCCCTGAAGGAGAAGTACGACAGCGCGGCGGCCATGCGGCTCAACAGC
CGGGGCAAGTTGGTACAGGTCAACAGCCGCTTCAACTCGCCCACCACACAAGACCTGG
TCTACATCGACCCCAGCCCTGACTACTGCGTGCGCAATGAGAGCACCGGCTCGCTGGG
CACGCAGGGCCGCCTGTGCAACAAGACGTCGGAGGGCATGGATGGCTGCGAGCTCATG
TGCTGCGGCCGTGGGTACGACCAGTTCAAGACCGTGCAGACGGAGCGCTGCCACTGCA
AGTTCCACTGGTGCTGCTACGTCAAGTGCAAGAAGTGCACGGAGATCGTGGACCAGTT
TGTGTGCAAGTAGTGGGTGCCACCCAGCACTCAGCCCCGCTCCCAGGACCCGCTTATTT
ATAGAAAGTACAGTGATTCTGGTTTTTGGTTTTTAGAAATATTTTTTATTTTTCCCCAAG
AATTGCAACCGGAACCATTTTTTTTCCTGTTACCATCTAAGAACTCTGTGGTTTATTATT
AATATTATAATTATTATTTGGCAATAATGGGGGTGGGAACCACGAAAAATATTTATTTT
GTGGATCTTTGAAAAGGTAATACAAGACTTCTTTTGGATAGTATAGAATGAAGGGGGA
AATAACACATACCCTAACTTAGCTGTGTGGGACATGGTACACATCCAGAAGGTAAAGA
AATACATTTTCTTTTTCTCAAATATGCCATCATATGGGATGGGTAGGTTCCAGTTGAAA
GAGGGTGGTAGAAATCTATTCACAATTCAGCTTCTATGACCAAAATGAGTTGTAAATTC
TCTGGTGCAAGATAAAAGGTCTTGGGAAAACAAAACAAAACAAAACAAACCTCCCTTC
CCCAGCAGGGCTGCTAGCTTGCTTTCTGCATTTTCAAAATGATAATTTACAATGGAAGG
ACAAGAATGTCATATTCTCAAGGAAAAAAGGTATATCACATGTCTCATTCTCCTCAAAT
ATTCCATTTGCAGACAGACCGTCATATTCTAATAGCTCATGAAATTTGGGCAGCAGGGA
GGAAAGTCCCCAGAAATTAAAAAATTTAAAACTCTTATGTCAAGATGTTGATTTGAAG
CTGTTATAAGAATTGGGATTCCAGATTTGTAAAAAGACCCCCAATGATTCTGGACACTA
GATTTTTTGTTTGGGGAGGTTGGCTTGAACATAAATGAAATATCCTGTATTTTCTTAGG
GATACTTGGTTAGTAAATTATAATAGTAGAAATAATACATGAATCCCATTCACAGGTTT
CTCAGCCCAAGCAACAAGGTAATTGCGTGCCATTCAGCACTGCACCAGAGCAGACAAC
CTATTTGAGGAAAAACAGTGAAATCCACCTTCCTCTTCACACTGAGCCCTCTCTGATTC
CTCCGTGTTGTGATGTGATGCTGGCCACGTTTCCAAACGGCAGCTCCACTGGGTCCCCT
TTGGTTGTAGGACAGGAAATGAAACATTAGGAGCTCTGCTTGGAAAACAGTTCACTAC
TTAGGGATTTTTGTTTCCTAAAACTTTTATTTTGAGGAGCAGTAGTTTTCTATGTTTTAA
TGACAGAACTTGGCTAATGGAATTCACAGAGGTGTTGCAGCGTATCACTGTTATGATCC
TGTGTTTAGATTATCCACTCATGCTTCTCCTATTGTACTGCAGGTGTACCTTAAAACTGT
TCCCAGTGTACTTGAACAGTTGCATTTATAAGGGGGGAAATGTGGTTTAATGGTGCCTG
ATATCTCAAAGTCTTTTGTACATAACATATATATATATATACATATATATAAATATAAA
TATAAATATATCTCATTGCAGCCAGTGATTTAGATTTACAGCTTACTCTGGGGTTATCTC
TCTGTCTAGAGCATTGTTGTCCTTCACTGCAGTCCAGTTGGGATTATTCCAAAAGTTTTT
TGAGTCTTGAGCTTGGGCTGTGGCCCCGCTGTGATCATACCCTGAGCACGACGAAGCA
ACCTCGTTTCTGAGGAAGAAGCTTGAGTTCTGACTCACTGAAATGCGTGTTGGGTTGAA
GATATCTTTTTTTCTTTTCTGCCTCACCCCTTTGTCTCCAACCTCCATTTCTGTTCACTTT
GTGGAGAGGGCATTACTTGTTCGTTATAGACATGGACGTTAAGAGATATTCAAAACTC
AGAAGCATCAGCAATGTTTCTCTTTTCTTAGTTCATTCTGCAGAATGGAAACCCATGCC
TATTAGAAATGACAGTACTTATTAATTGAGTCCCTAAGGAATATTCAGCCCACTACATA
GATAGCTTTTTTTTTTTTTTTTTTTTAATAAGGACACCTCTTTCCAAACAGGCCATCA

AATATGTTCTTATCTCAGACTTACGTTGTTTTAAAAGTTTGGAAAGATACACATCTTTTC
ATACCCCCCCTTAGGAGGTTGGGCTTTCATATCACCTCAGCCAACTGTGGCTCTTAATT
TATTGCATAATGATATCCACATCAGCCAACTGTGGCTCTTTAATTTATTGCATAATGAT
ATTCACATCCCCTCAGTTGCAGTGAATTGTGAGCAAAAGATCTTGAAAGCAAAAAGCA
CTAATTAGTTTAAAATGTCACTTTTTTGGTTTTTATTATACAAAAACCATGAAGTACTTT
TTTTATTTGCTAAATCAGATTGTTCCTTTTTAGTGACTCATGTTTATGAAGAGAGTTGAG
TTTAACAATCCTAGCTTTTAAAAGAAACTATTTAATGTAAAATATTCTACATGTCATTC
AGATATTATGTATATCTTCTAGCCTTTATTCTGTACTTTTAATGTACATATTTCTGTCTTG
CGTGATTTGTATATTTCACTGGTTTAAAAAACAAACATCGAAAGGCTTATTCCAAATGG
AAG

Figure 41

MAGSAMSSKFFLVALAIFFSFAQVVIEANSWWSLGMNNPVQMSEVYIIGAQPLCSQLAGLS
QGQKKLCHLYQDHMQYIGEGAKTGIKECQYQFRHRRWNCSTVDNTSVFGRVMQIGSRET
AFTYAVSAAGVVNAMSRACREGELSTCGCSRAARPKDLPRDWLWGGCGDNIDYGYRFA
KEFVDARERERIHAKGSYESARILMNLHNNEAGRRTVYNLADVACKCHGVSGSCSLKTC
WLQLADFRKVGDALKEKYDSAAAMRLNSRGKLVQVNSRFNSPTTQDLVYIDPSPDYCVR
NESTGSLGTQGRLCNKTSEGMDGCELMCCGRGYDQFKTVQTERCHCKFHWCCYVKCKK
CTEIVDQFVCK

Figure 42

GGCACGAGCGCAGGAGACACAGGCGCTGGCTGCCCCGTCCGCTCTCCGCCTCCGCCGC
GCCCTCCTCGCCCGGGATGGGCCCCCCGCCGCCGCCGGATCCCTCGCCTCCCGGCCGC
CGCCGTTGCGCTCGCCGCGCTCGCACTGAAGCCCGGGCCCTCGCGCGCCGCGGTTCGC
CCCGCAGCCTCGCCCCCTGCCCACCCGGGCGGCCGTAGGGCGGTCACGATGCTGCCGC
CCTTACCCTCCCGCCTCGGGCTGCTGCTGCTGCTGCTCCTGTGCCCGGCGCACGTCGGC
GGACTGTGGTGGGCTGTGGGCAGCCCCTTGGTTATGGACCCTACCAGCATCTGCAGGA
AGGCACGGCGGCTGGCCGGGCGGCAGGCCGAGTTGTGCCAGGCTGAGCCGGAAGTGG
TGGCAGAGCTAGCTCGGGGCGCCCGGCTCGGGGTGCGAGAGTGCCAGTTCCAGTTCCG
CTTCCGCCGCTGGAATTGCTCCAGCCACAGCAAGGCCTTTGGACGCATCCTGCAACAG
GACATTCGGGAGACGGCCTTCGTGTTCGCCATCACTGCGGCCGGCGCCAGCCACGCCG
TCACGCAGGCCTGTTCTATGGGCGAGCTGCTGCAGTGCGGCTGCCAGGCGCCCCGCGG
GCGGGCCCCTCCCCGGCCCTCCGGCCTGCCCGGCACCCCCGGACCCCCTGGCCCCGCG
GGCTCCCCGGAAGGCAGCGCCGCCTGGGAGTGGGGAGGCTGCGGCGACGACGTGGAC
TTCGGGGACGAGAAGTCGAGGCTCTTTATGGACGCGCGGCACAAGCGGGGACGCGGA
GACATCCGCGCGTTGGTGCAACTGCACAACAACGAGGCGGGCAGGCTGGCCGTGCGG
AGCCACACGCGCACCGAGTGCAAATGCCACGGGCTGTCGGGATCATGCGCGCTGCGCA
CCTGCTGGCAGAAGCTGCCTCCATTTCGCGAGGTGGGCGCGCGGCTGCTGGAGCGCTT
CCACGGCGCCTCACGCGTCATGGGCACCAACGACGGCAAGGCCCTGCTGCCCGCCGTC
CGCACGCTCAAGCCGCCGGGCCGAGCGGACCTCCTCTACGCCGCCGATTCGCCCGACT
TTTGCGCCCCCAACCGACGCACCGGCTCCCCCGGCACGCGCGGTCGCGCCTGCAATAG
CAGCGCCCCGGACCTCAGCGGCTGCGACCTGCTGTGCTGCGGCCGCGGGCACCGCCAG

GAGAGCGTGCAGCTCGAAGAGAACTGCCTGTGCCGCTTCCACTGGTGCTGCGTAGTAC
AGTGCCACCGTTGCCGTGTGCGCAAGGAGCTCAGCCTCTGCCTGTGACCCGCCGCC
CGGCCGCTAGACTGACTTCGCGCAGCGGTGGCTCGCACCTGTGGGACCTCAGGGCACC
GGCACCGGGCGCCTCTCGCCGCTCGAGCCCAGCCTCTCCCTGCCAAAGCCCAACTCCC
AGGGCTCTGGAAATGGTGAGGCGAGGGGCTTGAGAGGAACGCCCACCCACGAAGGCC
CAGGGCGCCAGACGGCCCCGAAAAGGCGCTCGGGGAGCGTTTAAAGGACACTGTACA
GGCCCTCCCTCCCCTTGGCCTCTAGGAGGAAACAGTTTTTAGACTGGAAAAAAGCCA
GTCTAAAGGCCTCTGGATACTGGGCTCCCCAGAACTGCTGGCCACAGGATGGTGGGTG
AGGTTAGTATCAATAAAGATATTTAAACCAAAAAAAAAAAAAAAAAAAA

Figure 43

MLPPLPSRLGLLLLLLLCPAHVGGLWWAVGSPLVMDPTSICRKARRLAGRQAELCQAEPE
VVAELARGARLGVRECQFQFRFRRWNCSSHSKAFGRILQQDIRETAFVFAITAAGASHAVT
QACSMGELLQCGCQAPRGRAPPRPSGLPGTPGPPGPAGSPEGSAAWEWGGCGDDVDFGD
EKSRLFMDARHKRGRGDIRALVQLHNNEAGRLAVRSHTRTECKCHGLSGSCALRTCWQK
LPPFREVGARLLERFHGASRVMGTNDGKALLPAVRTLKPPGRADLLYAADSPDFCAPNRR
TGSPGTRGRACNSSAPDLSGCDLLCCGRGHRQESVQLEENCLCRFHWCCVVQCHRCRVRK
ELSLCL

Figure 44

CACGCGTCCGGGCCAATCGGGACTATGAACCGGAAAGCGCTGCGCTGCCTGGGCCACC
TCTTTCTCAGCCTGGGCATGGTCTGCCTCCGGATCGGTGGCTTCTCCTCAGTGGTAGCTC
TGGGCGCAACGATCATCTGTAACAAGATCCCAGGCCTGGCTCCCAGACAGCGGGCGAT
CTGCCAGAGCCGGCCCGACGCCATCATCGTCATAGGAGAAGGCTCACAAATGGGCCTG
GACGAGTGTCAGTTTCAGTTCCGCAATGGCCGCTGGAACTGCTCTGCACTGGGAGAGC
GCACCGTCTTCGGGAAGGAGCTCAAAGTGGGGAGCCGGGACGGTGCGTTCACCTACGC
CATCATTGCCGCCGGCGTGGCCCACGCCATCACAGCTGCCTGTACCCATGGCAACCTG
AGCGACTGTGGCTGCGACAAAGAGAAGCAAGGCCAGTACCACCGGGACGAGGGCTGG
AAGTGGGGTGGCTGCTCTGCCGACATCCGCTACGGCATCGGCTTCGCCAAGGTCTTTGT
GGATGCCCGGGAGATCAAGCAGAATGCCCGGACTCTCATGAACTTGCACAACAACGAG
GCAGGCCGAAAGATCCTGGAGGAGAACATGAAGCTGGAATGTAAGTGCCACGGCGTG
TCAGGCTCGTGCACCACCAAGACGTGCTGGACCACACTGCCACAGTTTCGGGAGCTGG
GCTACGTGCTCAAGGACAAGTACAACGAGGCCGTTCACGTGGAGCCTGTGCGTGCCAG
CCGCAACAAGCGGCCCACCTTCCTGAAGATCAAGAAGCCACTGTCGTACCGCAAGCCC
ATGGACACGGACCTGGTGTACATCGAGAAGTCGCCCAACTACTGCGAGGAGGACCCGG
TGACCGGCAGTGTGGGCACCCAGGGCCGCGCCTGCAACAAGACGGCTCCCCAGGCCAG
CGGCTGTGACCTCATGTGCTGTGGGCGTGGCTACAACACCCACCAGTACGCCCGCGTG
TGGCAGTGCAACTGTAAGTTCCACTGGTGCTGCTATGTCAAGTGCAACACGTGCAGCG
AGCGCACGGAGATGTACACGTGCAAGTGAGCCCCGTGTGCACACCACCCTCCCGCTGC
AAGTCAGATTGCTGGGAGGACTGGACCGTTTCCAAGCTGCGGGCTCCCTGGCAGGATG
CTGAGCTTGTCTTTTCTGCTGAGGAAGGTACTTTTCCTGGGTTTCCTGCAGGCATCCGTG
GGGGAAAAAAAATCTCTCAGAACCCTCAACTATTCTGTTCCACACCCAATGCTGCTCCA
CCCTCCCCCAGACACAGCCCAAGTCCCTCCGCGGCTGGAGCGAAGCCTTCTGCAGCAG
GAACTCTGGACCCCTGGGCCTCATCACAGCAATATTTAACAATTTATTCTGATAAAAT
AATATTAATTTATTTAATTAAAAAGAATTCTTCCACCTCAAAAAAAAAAAAAAAAAAA
AAAAAAAAGGGGGG

Figure 45

MNRKARRCLGHLFLSLGMVYLRIGGFSSVVALGASIICNKIPGLAPRQRAICQSRPDAIIVIG
EGSQMGLDECQFQFRNGRWNCSALGERTVFGKELKVGSREAAFTYAIIAAGVAHAITAAC
TQGNLSDCGCDKEKQGQYHRDEGWKWGGCSADIRYGIGFAKVFVDAREIKQNARTLMNL
HNNEAGRKILEENMKLECKCHGVSGSCTTKTCWTTLPQFRELGYVLKDKYNEAVHVEPV
RASRNKRPTFLKIKKPLSYRKPMDTDLVYIEKSPNYCEEDPVTGSVGTQGRACNKTAPQAS
GCDLMCCGRGYNTHQYARVWQCNCKFHWCCYVKCNTCSERTEMYTCK

Figure 46

MHRNFRKWIFYVFLCFGVLYVKLGALSSVVALGANIICNKIPGLAPRQRAICQSRPDAIIVIG
EGAQMGINECQYQFRFGRWNCSALGEKTVFGQELRVGSREAAFTYAITAAGVAHAVTAA
CSQGNLSNCGCDREKQGYYNQAEGWKWGGCSADVRYGIDFSRRFVDAREIKKNARRLM
NLHNNEAGRKVLEDRMQLECKCHGVSGSCTTKTCWTTLPKFREVGHLLKEKYNAAVQVE
VVRASRLRQPTFLRIKQLRSYQKPMETDLVYIEKSPNYCEEDAATGSVGTQGRLCNRTSPG
ADGCDTMCCGRGYNTHQYTKVWQCNCKFHWCCFVKCNTCSERTEVFTCK

Figure 47

TCCGCTTACACACCAAGGAAAGTTGGGCTTTGAAGAATTCCATCCCCATGGCCACTGG
AGGAAGAATATTTCNCCCGTCTTGCTTACCCATCTCCCCAGTTTTTGGAATTTTCTCTA
GCTGTTACTCCAGAGGATTATGTTTCTTTCAAAGCCTTCTGTGTACATCTGTCTTTTCAC
CTGTGTCCTCCAACTCAGCCACAGCTGGTCGGTGAACAATTTCCTGATGACTGGTCCAA
AGGCTTACCTGATTTACTCCAGCAGTGTGGCAGCTGGTGCCCAGAGTGGTATTGAAGA
ATGCAAGTATCAGTTTGCCTGGGACCGCTGGAACTGCCCTGAGAGAGCCCTGCAGCTG
TCCAGCCATGGTGGGCTTCGCAGTGCCAATCGGGAGACAGCATTTGTGCATGCCATCA
GTTCTGCTGGAGTCATGTACACCCTGACTAGAAACTGCAGCCTTGGAGATTTTGATAAC
TGTGGCTGTGATGACTCCCGCAACGGGCAACTGGGGGGACAAGGCTGGCTGTGGGGAG
GCTGCAGTGACAATGTGGGCTTCGGAGAGGCGATTTCCAAGCAGTTTGTCGATGCCCT
GGAAACAGGACAGGATGCACGGGCAGCCATGAACCTGCACAACAACGAGGCTGGCCG
CAAGGCGGTGAAGGGCACCATGAAACGCACGTGTAAGTGCCATGGCGTGTCTGGCAGC
TGCACCACGCAGACCTGTTGGCTGCAGCTGCCCGAGTTCCGCGAGGTGGGCGCGCACC
TGAAGGAGAAGTACCACGCAGCACTCAAGGTGGACCTGCTGCAGGGTGCTGGCAACA
GCGCGGCCGCCCGCGGCGCCATCGCCGACACCTTTCGCTCCATCTCTACCCGGGAGCTG
GTGCACCTGGAGGACTCCCCGGACTACTGCCTGGAGAACAAAACGCTAGGGCTGCTGG
GCACCGAAGGCCGAGAGTGCCTAAGGCGCGGGCGGGCCCTGGGTCGCTGGGAACTCC
GCAGCTGCCGCCGGCTCTGCGGGGACTGCGGGCTGGCGGTGGAGGAGCGCCGGGCCG
AGACCGTGTCCAGCTGCAACTGCAAGTTCCACTGGTGCTGTGCAGTCCGCTGCGAGCA
GTGCCGCCGGAGGGTCACCAAGTACTTCTGTAGCCGCGCAGAGCGGCCGCGGGGGGC
GCTGCGCACAAACCCGGGAGAAAACCCTAAGGGTTTCCTCTGCCCCCTCCTTTTCCCAC
TGGTTCTTGGCTTCCTTTAGAGACCCCGGTAATTGTGGAACCTAGGGAATGGGGAACCC
GCTCTCCCAGACCTAGGGATCCTGAAAGGGAAAAACTGCAATTTCTCCAAAGCTTGCC
ACTTTCCAGCCTGTTTCCCCAATTCCTCTGTGCTCTCCTAAAGCTCTGTCTGAATCCTCG
CAGCCACACCTAGGTCTGAAAACTCAGGCTTTGAGTTACTGATCTTCCTTGGATTAGGA
AAACAGGTGTTCCTCCTCCCCTCTCCTATCAGCCCTAATCTCTGACCTAGCCTATCAAC
GCTTAGGCCCCTGGAAAAACCTTCTCATACACGCAGGACCCAGGTTAACTCAAAGCTTT

GCCCTTTTGCCCACTGTCTGCTACCAGGGGCTCACCCTCTGCTGCACCTCTCTTCTGCAC
AGCTCCTCCCCTGCTACTGCTGACCAAATTCCCAGGAATCTTGAATGCTTTCTCTCCTCT
TCTCCCTTTCCTTTCCCAAAAAAAACTGAGGAAACTGGCCCCGGAAAAGCATGTCTTTG
GGGTTGGTTCCTAGAGGCAGAGGTTGAAGATGGAAGAGGGAGCTCTGGAGTGCTAACT
TGAACACCAAGGGTGCTACTCATCCCTATGGTATCATATCATGAATGGACTTTACTAGT
GGGGCAATGACTTTCCTAGACAATAACCCGAGGGACTCCAGATACATACCCCGAAGGT
CTAGGAAATACGTTAAGGGCAGATTACAGTCATTTCCTACCCTTTAAAGGTAACTTCTC
CCTTCTCCTGACCTACTTCCTCCTAGCAACCAACTTTACCTCTTCTTCTCCAAAGGATCT
TTGTTCCTCTGAGCCAAGACTGAGGTAAATAAAGCCACTTTCCTCTTCAGATCCTGGTC
TGCACCTCTAGA

Figure 48

MFLSKPSVYICLFTCVLQLSHSWSVNNFLMTGPKAYLIYSSSVAAGAQSGIEECKYQFAWD
RWNCPERALQLSSHGGLRSANRETAFVHAISSAGVMYTLTRNCSLGDFDNCGCDDSRNGQ
LGGQGWLWGGCSDNVGFGEAISKQFVDALETGQDARAAMNLHNNEAGRKAVKGTMKR
TCKCHGVSGSCTTQTCWLQLPEFREVGAHLKEKYHAALKVDLLQGAGNSAAARGAIADT
FRSISTRELVHLEDSPDYCLENKTLGLLGTEGRECLRRGRALGRWELRSCRRLCGDCGLAV
EERRAETVSSCNCKFHWCCAVRCEQCRRRVTKYFCSRAERPRGGAAHKPGRKP

Figure 49

GCGGCCGCGTCGACGGAGGGGCTGCAGCTCCGTCAGCCCGGCAGAGCCACCCTGAGCT
CGGTGAGAGCAAAGCCAGAGCCCCCAGTCCTTTGCTCGCCGGCTTGCTATCTCTCTCGA
TCACTCCCTCCCTTCCTCCCTCCCTTCCTCCCGGCGGCCGCGGCGGCGCTGGGGAAGCG
GTGAAGAGGAGTGGCCCGGCCCTGGAAGAATGCGGCTCTGACAAGGGGACAGAACCC
AGCGCAGTCTCCCCACGGTTTAAGCAGCACTAGTGAAGCCCAGGCAACCCAACCGTGC
CTGTCTCGGACCCCGCACCCAAACCACTGGAGGTCCTGATCGATCTGCCCACCGGAGC
CTCCGGGCTTCGACATGCTGGAGGAGCCCCGGCCGCGGCCTCCGCCCTCGGGCCTCGC
GGGTCTCCTGTTCCTGGCGTTGTGCAGTCGGGCTCTAAGCAATGAGATTCTGGGCCTGA
AGTTGCCTGGCGAGCCGCCGCTGACGGCCAACACCGTGTGCTTGACGCTGTCCGGCCT
GAGCAAGCGGCAGCTAGACCTGTGCCTGCGCAACCCCGACGTGACGGCGTCCGCGCTT
CAGGGTCTGCACATCGCGGTCCACGAGTGTCAGCACCAGCTGCGCGACCAGCGCTGGA
ACTGCTCCGCGCTTGAGGGCGGCGGCCGCCTGCCGCACCACAGCGCCATCCTCAAGCG
CGGTTTCCGAGAAAGTGCTTTTTCCTTCTCCATGCTGGCTGCTGGGGTCATGCACGCAG
TAGCCACGGCCTGCAGCCTGGGCAAGCTGGTGAGCTGTGGCTGTGGCTGGAAGGGCAG
TGGTGAGCAGGATCGGCTGAGGGCCAAACTGCTGCAGCTGCAGGCACTGTCCCGAGGC
AAGAGTTTCCCCCACTCTCTGCCCAGCCCTGGCCCTGGCTCAAGCCCCAGCCCTGGCCC
CCAGGACACATGGGAATGGGGTGGCTGTAACCATGACATGGACTTTGGAGAGAAGTTC
TCTCGGGATTTCTTGGATTCCAGGGAAGCTCCCCGGGACATCCAGGCACGAATGCGAA
TCCACAACAACAGGGTGGGGCGCCAGGTGGTAACTGAAAACCTGAAGCGGAAATGCA
AGTGTCATGGCACATCAGGCAGCTGCCAGTTCAAGACATGCTGGAGGGCGGCCCCAGA
GTTCCGGGCAGTGGGGGCGGCGTTGAGGGAGCGGCTGGGCCGGGCCATCTTCATTGAT
ACCCACAACCGCAATTCTGGAGCCTTCCAGCCCCGTCTGCGTCCCCGTCGCCTCTCAGG
AGAGCTGGTCTACTTTGAGAAGTCTCCTGACTTCTGTGAGCGAGACCCCACTATGGGCT
CCCCAGGGACAAGGGGCCGGGCCTGCAACAAGACCAGCCGCCTGTTGGATGGCTGTGG
CAGCCTGTGCTGTGGCCGTGGGCACAACGTGCTCCGGCAGACACGAGTTGAGCGCTGC
CATTGCCGCTTCCACTGGTGCTGCTATGTGCTGTGTGATGAGTGCAAGGTTACAGAGTG
GGTGAATGTGTGTAAGTGAGGGTCAGCCTTACCTTGGGGCTGGGGAAGAGGACTGTGT
GAGAGGGGCGCCTTTTCAGCCCTTTGCTCTGATTTCCTTCCAAGGTCACTCTTGGTCCCT

GGAAGCTTAAAGTATCTACCTGGAAACAGCTTTAGGGGTGGTGGGGGTCAGGTGGACT
CTGGGATGTGTAGCCTTCTCCCCAACAATTGGAGGGTCTTGAGGGGAAGCTGCCACCC
CTCTTCTGCTCCTTAGACACCTGAATGGACTAAGATGAAATGCACTGTATTGCTCCTCC
CACTTCTCAACTCCAGAGCCCCTTTAACCCTGATTCATACTCCTTTTGGCTGGGGAGTC
CCTATAGTTTCACCACTCCTCTCCCTTGAGGGATAACCCCAGGCACTGTTTGGAGCCAT
AAGATCTGTATCTAGAAAGAGATCACCCACTCCTATGTACTATCCCCAAACTCCTTTAC
TGCAGCCTGGGCTCCCTCTTGTGGGATAATGGGAGACAGTGGTAGAGAGGTTTTTCTTG
GGAAAGAGACAGAGTGCTGAGGGGCACTCTCCCCTGAATCCTCAGAGAGTTGTCTGTC
CAGGCCCTTAGGGAAGTTGTCTCCTTCCATTCAGATGTTAATGGGGACCCTCCAAAGGA
AGGGGTTTTCCCATGACTCTTGGAGCCTCTTTTTCCTTCTTCAGCAGGAAGGGTGGGAA
GGGATAATTTATCATACTGAGACTTGTTCTTGGTTCCTGTTTGAAACTAAAATAAATTA
AGTTACTGGAAAAAAAAAAAAAAAAA

Figure 50

MLEEPRPRPPPSGLAGLLFLALCSRALSNEILGLKLPGEPPLTANTVCLTLSGLSKRQLDLCL
RNPDVTASALQGLHIAVHECQHQLRDQRWNCSALEGGGRLPHHSAILKRGFRESAFSFSM
LAAGVMHAVATACSLGKLVSCGCGWKGSGEQDRLRAKLLQLQALSRGKSFPHSLPSPGP
GSSPSPGPQDTWEWGGCNHDMDFGEKFSRDFLDSREAPRDIQARMRIHNNRVGRQVVTEN
LKRKCKCHGTSGSCQFKTCWRAAPEFRAVGAALRERLGRAIFIDTHNRNSGAFQPRLRPRR
LSGELVYFEKSPDFCERDPTMGSPGTRGRACNKTSRLLDGCGSLCCGRGHNVLRQTRVER
CHCRFHWCCYVLCDECKVTEWVNVCK

Figure 51

TAACCCGCCGCCTCCGCTCTCCCCGGCTGCAGGCGGCGTGCAGGACCAGCGGCGGCCG
TGCAGGCGGAGGACTTCGGCGCGGCTCCTCCTGGGTGTGACCCCGGGCGCGCCCGCCG
CGCGACGATGAGGGCGCGGCCGCAGGTCTGCGAGGCGCTGCTCTTCGCCCTGGCGCTC
CAGACCGGCGTGTGCTATGGCATCAAGTGGCTGGCGCTGTCCAAGACACCATCGGCCC
TGGCACTGAACCAGACGCAACACTGCAAGCAGCTGGAGGGTCTGGTGTCTGCACAGGT
GCAGCTGTGCCGCAGCAACCTGGAGCTCATGCACACGGTGGTGCACGCCGCCCGCGAG
GTCATGAAGGCCTGTCGCCGGGCCTTTGCCGACATGCGCTGGAACTGCTCCTCCATTGA
GCTCGCCCCCAACTATTTGCTTGACCTGGAGAGAGGGACCCGGGAGTCGGCCTTCGTG
TATGCGCTGTCGGCCGCCACCATCAGCCACGCCATCGCCCGGGCCTGCACCTCCGGCG
ACCTGCCCGGCTGCTCCTGCGGCCCCGTCCCAGGTGAGCCACCCGGGCCCGGGAACCG
CTGGGGAAGATGTGCGGACAACCTCAGCTACGGGCTCCTCATGGGGGCCAAGTTTTCC
GATGCTCCTATGAAGGTGAAAAAAACAGGATCCCAAGCCAATAAACTGATGCGTCTAC
ACAACAGTGAAGTGGGGAGACAGGCTCTGCGCGCCTCTCTGGAAATGAAGTGTAAGTG
CCATGGGGTGTCTGGCTCCTGCTCCATCCGCACCTGCTGGAAGGGGCTGCAGGAGCTG
CAGGATGTGGCTGCTGACCTCAAGACCCGATACCTGTCGGCCACCAAGGTAGTGCACC
GACCCATGGGCACCCGCAAGCACCTGGTGCCCAAGGACCTGGATATCCGGCCTGTGAA
GGACTGGGAACTTGTTTATTTGCAGAGCTCACCTGACTTTTGCATGAAGAATGAGAAG
GTGGGCTCCCACGGGACACAAGACAGGCAGTGCAACAAGACTTCCAACGGAAGCGAC
AGCTGCGACCTTATGTGCTGCGGGCGTGGCTACAACCCCTACACAGACCGCGTGGTCG
AGCGGTGCCACTGTAAGTACCACTGGTGTTGCTACGTCACCTGCCGCAGGTGTGAGCGT
ACCGTGGAGCGCTATGTCTGCAAGTGAGGCCCTGCCCTCCGCCCCACGCAGGAGCGAG
GACTTTGCTCAAGGACCCTCAGCAACTGGGGCCGGGGGCCTGGAGACACTCCATGGAG
CTCTGCTTGTGAATTCCAGATGCCAGGCATGGGAGGCGGCTTGTGCTTTGCCTTCACTT
GGAAGCCACCAGGAACAGAAGGTCTGGCCACCCTGGAAGGAGNGCAGGACATCAAAG
GAAACCGACAAGATTAAAAATAACTTGGCAGCCTGAGNTCTGGAGTGCCCACAGNNTG

GTGTAAGGAGCGGGGCTTGGGATCGGTGAGACTGATACAGACTTGACCTTTCAGGGCC
ACAGAGACCAGCCTCCGGGAAGGGGTCTGCCCGCCTTCTTCAGAATGTTCTGCGGGAC
CCCCTGGCCCACCCTGGGGTCTGAGCCTGCTGGGCCACCACATGGAATCACTAGCTTCG
GGTTGTAAATGTTTTCTTTTGTTTNTTGCTTTTTCTTCCTTTGGGATGTTGGAAGCTACA
GAAATATTTATAAAACATAGCTTTTTCTTTGGGGTGGCACTTCTCAATTCCTCTTTATAT
ATTTTANATATATAAATATATATGTATATATATAATGATCTCTAATNTAAAACTAGCTT
TTTAAGCAGCTGTATGAAATAAATGCTGAGTGAGCCCCAGCCCGCCCCTGCAGTTCCC
GGCCTCGTCAAGTGAACTCGGCAGACCCTGGGGCTGGCAGAGGGAGCTCTCCAGTTTC
CGGGCA

Figure 52

MRARPQVCEALLFALALQTGVCYGIKWLALSKTPSALALNQTQHCKQLEGLVSAQVQLCR
SNLELMHTVVHAAREVMKACRRAFADMRWNCSSIELAPNYLLDLERGTRESAFVYALSA
ATISHAIARACTSGDLPGCSCGPVPGEPPGPGNRWGRCADNLSYGLLMGAKFSDAPMKVK
KTGSQANKLMRLHNSEVGRQALRASLEMKCKCHGVSGSCSIRTCWKGLQELQDVAADLK
TRYLSATKVVHRPMGTRKHLVPKDLDIRPVKDWELVYLQSSPDFCMKNEKVGSHGTQDR
QCNKTSNGSDSCDLMCCGRGYNPYTDRVVERCHCKYHWCCYVTCRRCERTVERYVCK

Figure 53

GGCGCGGCAAGATGCTGGATGGGTCCCCGCTGGCGCGCTGGCTGGCCGCGGCCTTCGG
GCTGACGCTGCTGCTCGCCGCGCTGCGCCCTTCGGCCGCCTACTTCGGGCTGACGGGCA
GCGAGCCCCTGACCATCCTCCCGCTGACCCTGGAGCCAGAGGCGGCCGCCCAGGCGCA
CTACAAGGCCTGCGACCGGCTGAAGCTGGAGCGGAAGCAGCGGCGCATGTGCCGCCG
GGACCCGGGCGTGGCAGAGACGCTGGTGGAGGCCGTGAGCATGAGTGCGCTCGAGTG
CCAGTTCCAGTTCCGCTTTGAGCGCTGGAACTGCACGCTGGAGGGCCGCTACCGGGCC
AGCCTGCTCAAGCGAGGCTTCAAGGAGACTGCCTTCCTCTATGCCATCTCCTCGGCTGG
CCTGACGCACGCACTGGCCAAGGCGTGCAGCGCGGGCCGCATGGAGCGCTGTACCTGC
GATGAGGCACCCGACCTGGAGAACCGTGAGGCCTGGCAGTGGGGGGGCTGCGGAGAC
AACCTTAAGTACAGCAGCAAGTTCGTCAAGGAATTCCTGGGCAGACGGTCAAGCAAGG
ATCTGCGAGCCCGTGTGGACTTCCACAACAACCTCGTGGGTGTGAAGGTGATCAAGGC
TGGGGTGGAGACCACCTGCAAGTGCCACGGCGTGTCAGGCTCATGCACGGTGCGGACC
TGCTGGCGGCAGTTGGCGCCTTTCCATGAGGTGGGCAAGCATCTGAAGCACAAGTATG
AGACGGCACTCAAGGTGGGCAGCACCACCAATGAAGCTGCCGGCGAGGCAGGTGCCA
TCTCCCCACCACGGGGCCGTGCCTCGGGGGCAGGTGGCAGCGACCCGCTGCCCCGCAC
TCCAGAGCTGGTGCACCTGGATGACTCGCCTAGCTTCTGCCTGGCTGGCCGCTTCTCCC
CGGGCACCGCTGGCCGTAGGTGCCACCGTGAGAAGAACTGCGAGAGCATCTGCTGTGG
CCGCGGCCATAACACACAGAGCCGGGTGGTGACAAGGCCCTGCCAGTGCCAGGTGCGT
TGGTGCTGCTATGTGGAGTGCAGGCAGTGCACGCAGCGTGAGGAGGTCTACACCTGCA
AGGGCTGAGTTCCCAGGCCCTGCCAGCCCTGCTGCACAGGGTGCAGGCATTGCACACG
GTGTGAAGGGTCTACACCTGCACAGGCTGAGTTCCTGGGCTCGACCAGCCCAGCTGCG
TGGGGTACAGGCATTGCACACAGTGTGAATGGGTCTACACCTGCATGGGCTGAGTCCC
TGGGCTCAGACCTAGCAGCGTGGGGTAGTCCCTGGGCTCAGTCCTAGCTGCATGGGGT
GCAGGCATTGCACAGAGCATGAATGGGCCTACACCTGCCAAGGCTGAATCCCTGGGCC
CAGCCAGCCCTGCTGCACATGGCACAGGCATTGCACACGGTGTGAGGAGTGTACACCT
GCAAGGGCTGAGGCCCTGGGCCCAGTCAGCCCTGCTGCTCAGAGTGCAGGCATTGCAC
ATGGTGTGAGAAGGTCTACACCTGCAAGGGACGAGTCCCCGGGCCTGGCCAACCCTGC
TGTGCAGGGTGAGGGCCATGCATGCTAGTATGAGGGGTCTACACCTGCAAGGACTGAG
AGGCTTTT

Figure 54

MLDGSPLARWLAAAFGLTLLLAALRPSAAYFGLTGSEPLTILPLTLEPEAAAQAHYKACDR
LKLERKQRRMCRRDPGVAETLVEAVSMSALECQFQFRFERWNCTLEGRYRASLLKRGFKE
TAFLYAISSAGLTHALAKACSAGRMERCTCDEAPDLENREAWQWGGCGDNLKYSSKFVK
EFLGRRSSKDLRARVDFHNNLVGVKVIKAGVETTCKCHGVSGSCTVRTCWRQLAPFHEVG
KHLKHKYETALKVGSTTNEAAGEAGAISPPRGRASGAGGSDPLPRTPELVHLDDSPSFCLA
GRFSPGTAGRRCHREKNCESICCGRGHNTQSRVVTRPCQCQVRWCCYVECRQCTQREEVY
TCKG

Figure 55

AGCCTGCAAAAACCACAGAGGGCAAAGCCAGAAAGATGGAAAGGCACCCACCCATGC
AGCTCACCACTTGCCTCAGGGAGACCCTCTTCACAGGGGCTTCTCAAAAGACCTCCCTA
TGGTGGTTGGGCATTGCCTCCTTCGGGGTTCCAGAGAAGCTGGGCTGCGCCAATTTGCC
GCTGAACAGCCGCCAGAAGGAGCTGTGCAAGAGGAAACCGTACCTGCTGCCGAGCAT
CCGAGAGGGCGCCCGGCTGGGCATTCAGGAGTGCAGGAGCCAGTTCAGACACGAGAG
ATGGAACTGCATGATCACCGCCGCCGCCACTACCGCCCCGATGGGCGCCAGCCCCCTC
TTTGGCTACGAGCTGAGCAGCGGCACCAAAGAGACAGCATTTATTTATGCTGTGATGG
CTGCAGGCCTGGTGCATTCTGTGACCAGGTCATGCAGTGCAGGCAACATGACAGAGTG
TTCCTGTGACACCACCTTGCAGAACGGCGGCTCAGCAAGTGAAGGCTGGCACTGGGGG
GGCTGCTCCGATGATGTCCAGTATGGCATGTGGTTCAGCAGAAAGTTCCTAGATTTCCC
CATCGGAAACACCACGGGCAAAGAAAACAAAGTACTATTAGCAATGAACCTACATAA
CAATGAAGCTGGAAGGCAGGCTGTCGCCAAGTTGATGTCAGTAGACTGCCGCTGCCAC
GGAGTTTCCGGCTCCTGTGCTGTGAAAACATGCTGGAAAACCATGTCTTCTTTTGAAAA
GATTGGCCATTTGTTGAAGGATAAATATGAAAACAGTATCCAGATATCAGACAAAATA
AAGAGGAAAATGCGCAGGAGAGAAAAAGATCAGAGGAAAATACCAATCCATAAGGAT
GATCTGCTCTATGTTAATAAGTCTCCCAACTACTGTGTAGAAGATAAGAAACTGGGAAT
CCCAGGGACACAAGGCAGAGAATGCAACCGTACATCAGAGGGTGCAGATGGCTGCAA
CCTCCTCTGCTGTGGCCGAGGTTACAACACCCATGTGGTCAGGCACGTGGAGAGGTGT
GAGTGTAAGTTCATCTGGTGCTGCTATGTCCGTTGCAGGAGGTGTGAAAGCATGACTG
ATGTCCACACTTGCAAGTAACCACTCCATCCAGCCTTGGGCAAGATGCCTCAGCAATAT
ACAATGGCATTGCAACCAGAGAGGTGCCCATCCCTGTGCAGCGCTAGTAAAGTTGACT
CTTGCAGTGGAATCCC

Figure 56

MDRAALLGLARLCALWAALLVLFPYGAQGNWMWLGIASFGVPEKLGCANLPLNSRQKEL
CKRKPYLLPSIREGARLGIQECGSQFRHERWNCMITAAATTAPMGASPLFGYELSSGTKET
AFIYAVMAAGLVHSVTRSCSAGNMTECSCDTTLQNGGSASEGWHWGGCSDDVQYGMWF
SRKFLDFPIGNTTGKENKVLLAMNLHNNEAGRQAVAKLMSVDCRCHGVSGSCAVKTCWK
TMSSFEKIGHLLKDKYENSIQISDKTKRKMRRREKDQRKIPIHKDDLLYVNKSPNYCVEDK
KLGIPGTQGRECNRTSEGADGCNLLCCGRGYNTHVVRHVERCECKFIWCCYV
RCRRCESMTDVHTCK

Figure 57

AGTTGAGGGATTGACACAAATGGTCAGGCGGCGGCGGCGGAGAAGGAGGCGGAGGCG

CACTAGCGCGGCGCCGCCAGCCGGGAGCCAGCGAGCCGAGGGCCAGGAAGGCGGGAC
ACGACCCCGGCGCGCCCTAGCCACCCGGGTTCTCCCCGCCGCCCGCGCTTCATGAATCG
CAAGTTTCCGCGGCGGCGGCGGCTGCGGTACGCAGAACAGGAGCCGGGGGAGCGGGC
CGAAAGCGGCTTGGGCTCGACGGAGGGCACCCGCGCAGAGGTCTCCCTGGCCGCAGG
GGGAGCCGCCGCCGGCCGTGCCCCTGGCAGCCCCAGCGGAGCGGCGCCAAGAGAGGA
GCCGAGAAAGTATGGCTGAGGAGGAGGCGCCTAAGAAGTCCCGGGCCGCCGGCGGTG
GCGCGAGCTGGGAACTTTGTGCCGGGGCGCTCTCGGCCCGGCTGGCGGAGGAGGGCAG
CGGGGACGCCGGTGGCCGCCGCCGCCCGCCAGTTGACCCCCGGCGATTGGCGCGCCAG
CTGCTGCTGCTGCTTTGGCTGCTGGAGGCTCCGCTGCTGCTGGGGGTCCGGGCCCAGGC
GGCGGGCCAGGGGCCAGGCCAGGGGCCCGGGCCGGGGCAGCAACCGCCGCCGCCGCC
TCAGCAGCAACAGAGCGGGCAGCAGTACAACGGCGAGCGGGGCATCTCCGTCCCGGA
CCACGGCTATTGCCAGCCCATCTCCATCCCGCTGTGCACGGACATCGCGTACAACCAG
ACCATCATGCCCAACCTGCTGGGCCACACGAACCAGGAGGACGCGGGCCTGGAGGTGC
ACCAGTTCTACCCTCTAGTGAAAGTGCAGTGTTCCGCTGAGCTCAAGTTCTTCCTGTGC
TCCATGTACGCGCCCGTGTGCACCGTGCTAGAGCAGGCGCTGCCGCCCTGCCGCTCCCT
GTGCGAGCGCGCGCGCCAGGGCTGCGAGGCGCTCATGAACAAGTTCGGCTTCCAGTGG
CCAGACACGCTCAAGTGTGAGAAGTTCCCGGTGCACGGCGCCGGCGAGCTGTGCGTGG
GCCAGAACACGTCCGACAAGGGCACCCCGACGCCCTCGCTGCTTCCAGAGTTCTGGAC
CAGCAACCCTCAGCACGGCGGCGGAGGGCACCGTGGCGGCTTCCCGGGGGGCGCCGG
CGCGTCGGAGCGAGGCAAGTTCTCCTGCCCGCGCGCCCTCAAGGTGCCCTCCTACCTCA
ACTACCACTTCCTGGGGGAGAAGGACTGCGGCGCACCTTGTGAGCCGACCAAGGTGTA
TGGGCTCATGTACTTCGGGCCCGAGGAGCTGCGCTTCTCGCGCACCTGGATTGGCATTT
GGTCAGTGCTGTGCTGCGCCTCCACGCTCTTCACGGTGCTTACGTACCTGGTGGACATG
CGGCGCTTCAGCTACCCGGAGCGGCCCATCATCTTCTTGTCCGGCTGTTACACGGCCGT
GGCCGTGGCCTACATCGCCGGCTTCCTCCTGGAAGACCGAGTGGTGTGTAATGACAAG
TTCGCCGAGGACGGGGCACGCACTGTGGCGCAGGGCACCAAGAAGGAGGGCTGCACC
ATCCTCTTCATGATGCTCTACTTCTTCAGCATGGCCAGCTCCATCTGGTGGGTGATCCTG
TCGCTCACCTGGTTCCTGGCGGCTGGCATGAAGTGGGGCCACGAGGCCATCGAAGCCA
ACTCACAGTATTTTCACCTGGCCGCCTGGGCTGTGCCGGCCATCAAGACCATCACCATC
CTGGCGCTGGGCCAGGTGGACGGCGATGTGCTGAGCGGAGTGTGCTTCGTGGGGCTTA
ACAACGTGGACGCGCTGCGTGGCTTCGTGCTGGCGCCCCTCTTCGTGTACCTGTTTATC
GGCACGTCCTTTCTGCTGGCCGGCTTTGTGTCGCTCTTCCGCATCCGCACCATCATGAA
GCACGATGGCACCAAGACCGAGAAGCTGGAGAAGCTCATGGTGCGCATTGGCGTCTTC
AGCGTGCTGTACACTGTGCCAGCCACCATCGTCATCGCCTGCTACTTCTACGAGCAGGC
CTTCCGGGACCAGTGGGAACGCAGCTGGGTGGCCCAGAGCTGCAAGAGCTACGCTATC
CCCTGCCCTCACCTCCAGGCGGGCGGAGGCGCCCCGCCGCACCCGCCCATGAGCCCGG
ACTTCACGGTCTTCATGATTAAGTACCTTATGACGCTGATCGTGGGCATCACGTCGGGC
TTCTGGATCTGGTCCGGCAAGACCCTCAACTCCTGGAGGAAGTTCTACACGAGGCTCA
CCAACAGCAAACAAGGGGAGACTACAGTCTGAGACCCGGGGCTCAGCCCATGCCCAG
GCCTCGGCCGGGGCGCAGCGATCCCCCAAAGCCAGCGCCGTGGAGTTCGTGCCAATCC
TGACATCTCGAGGTTTCCTCACTAGACAACTCTCTTTCGCAGGCTCCTTTGAACAACTC
AGCTCCTGCAAAAGCTTCCGTCCCTGAGGCAAAAGGACACGAGGGCCCGACTGCCAGA
GGGAGGATGGACAGACCTCTTGCCCTCACACTCTGGTACCAGGACTGTTCGCTTTTATG
ATTGTAAATAGCCTGTGTAAGATTTTTGTAAGTATATTTGTATTTAAATGACGACCGAT
CACGCGTTTTTCTTTTTCAAAAGTTTTTAATTATTTAGGGCGGTTTAACCATTTGAGGCT
TTTCCTTCTTGCCCTTTTCGGAGTATTGCAAAGGAGCTAAAACTGGTGTGCAACCGCAC
AGCGCTCCTGGTCGTCCTCGCGCGCCTCTCCCTACCACGGGTGCTCGGGACGGCTGGGC
GCCAGCTCCGGGGCGAGTTCAGCACTGCGGGGTGCGACTAGGGCTGCGCTGCCAGGGT
CACTTCCCGCCTCCTCCTTTTGCCCCCTCCCCCTCCTTCTGTCCCCTCCCTTTCTTTCCTG
GCTTGAGGTAGGGGCTCTTAAGGTACAGAACTCCACAAACCTTCCAAATCTGGAGGAG
GGCCCCCATACATTACAATTCCTCCCTTGCTCGGCGGTGGATTGCGAAGGCCCGTCCCT

CCACGGGTGTGGGCGCTGGCAGTCTCAGCCTCCCTCCACGGTCACCTTCAACGCCCAG
ACACTCCCTTCTCCCACCTTAGTTGGTTACAGGGTGAGTGAGATAACCAATGCCAAACT
TTTTGAAGTCTAATTTTTGAGGGGTGAGCTCATTTCATTCTCTAGTGTCTAAAACCTGGT
ATGGGTTTGGCCAGCGTCATGGAAAGATGTGGTTACTGAGATTTGGGAAGAAGCATGA
AGCTTTGTGTGGGTTGGAAGAGACTGAAGATATGGGTTATAAAATGTTAATTCTAATTG
CATACGGATGCCTGGCAACCTTGCCTTTGAGAATGAGACAGCCTGCGCTTAGATTTTAC
CGGTCTGTAAAATGGAAATGTTGAGGTCACCTGGAAAGCTTTGTTAAGGAGTTGATGTT
TGCTTTCCTTAACAAGACAGCAAAACGTAAACAGAAATTGAAAACTTGAAGGATATTT
CAGTGTCATGGACTTCCTCAAAATGAAGTGCTATTTTCTTATTTTTAATCAAATAACTA
GACATATATCAGAAACTTTAAAATGTAAAAGTTGTACACTTTCAACATTTTATTACGAT
TATTATTCAGCAGCACATTCTGAGGGGGGAACAATTCACACCACCAATAATAACCTGG
TAAGATTTCAGGAGGTAAAGAAGGTGGAATAATTGACGGGGAGATAGCGCCTGAAAT
AAACAAAATATGGGCATGCATGCTAAAGGGAAAATGTGTGCAGGTCTACTGCATTAAA
TCCTGTGTGCTCCTCTTTTGGATTTACAGAAATGTGTCAAATGTAAATCTTTCAAAGCC
ATTTAAAAATATTCACTTTAGTTCTCTGTGAAGAAGAGGAGAAAAGCAATCCTCCTGAT
TGTATTGTTTTAAACTTTAAGAATTTATCAAAATGCCGGTACTTAGGACCTAAATTTAT
CTATGTCTGTCATACGCTAAAATGATATTGGTCTTTGAATTTGGTATACATTTATTCTGT
TCACTATCACAAAATCATCTATATTTATAGAGGAATAGAAGTTTATATATATATAATAC
CATATTTTTAATTTCACAAATAAAAAATTCAAAGTTTTGTACAAAATTATATGGATTTT
GTGCCTGAAAATAATAGAGCTTGAGCTGTCTGAACTATTTTACATTTTATGGTGTCTCA
TAGCCAATCCCACAGTGTAAAAATTCA

Figure 58

MAEEEAPKKSRAAGGGASWELCAGALSARLAEEGSGDAGGRRRPPVDPRRLARQLLLLL
WLLEAPLLLGVRAQAAGQGPGQGPGPGQQPPPPPQQQQSGQQYNGERGISVPDHGYCQPI
SIPLCTDIAYNQTIMPNLLGHTNQEDAGLEVHQFYPLVKVQCSAELKFFLCSMYAPVCTVL
EQALPPCRSLCERARQGCEALMNKFGFQWPDTLKCEKFPVHGAGELCVGQNTSDKGTPTP
SLLPEFWTSNPQHGGGGHRGGFPGGAGASERGKFSCPRALKVPSYLNYHFLGEKDCGAPC
EPTKVYGLMYFGPEELRFSRTWIGIWSVLCCASTLFTVLTYLVDMRRFSYPERPIIFLSGCYT
AVAVAYIAGFLLEDRVVCNDKFAEDGARTVAQGTKKEGCTILFMMLYFFSMASSIWW
VILSLTWFLAAGMKWGHEAIEANSQYFHLAAWAVPAIKTITILALGQVDGDVLSGVCFVG
LNNVDALRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTIMKHDGTKTEKLEKLMVRIGVFSV
LYTVPATIVIACYFYEQA
FRDQWERSWVAQSCKSYAIPCPHLQAGGGAPPHPPMSPDFTVFMIKYLMTLIVGITSGFWI
WSGKTLNSW RKFYTRLTNSKQGETTV

Figure 59

CGAGTAAAGTTTGCAAAGAGGCGCGGGAGGCGGCAGCCGCAGCGAGGAGGCGGCGGG
GAAGAAGCGCAGTCTCCGGGTTGGGGGCGGGGGCGGGGGGGGCGCCAAGGAGCCGGG
TGGGGGGCGGCGGCCAGCATGCGGCCCCGCAGCGCCCTGCCCCGCCTGCTGCTGCCGC
TGCTGCTGCTGCCCGCCGCCGGGCCGGCCCAGTTCCACGGGGAGAAGGGCATCTCCAT
CCCGGACCACGGCTTCTGCCAGCCCATCTCCATCCCGCTGTGCACGGACATCGCCTACA
ACCAGACCATCATGCCCAACCTTCTGGGCCACACGAACCAGGAGGACGCAGGCCTAGA
GGTGCACCAGTTCTATCCGCTGGTGAAGGTGCAGTGCTCGCCCGAACTGCGCTTCTTCC
TGTGCTCCATGTACGCACCCGTGTGCACCGTGCTGGAACAGGCCATCCCGCCGTGCCGC
TCTATCTGTGAGCGCGCGCGCCAGGGCTGCGAAGCCCTCATGAACAAGTTCGGTTTTCA
GTGGCCCGAGCGCCTGCGCTGCGAGCACTTCCCGCGCCACGGCGCCGAGCAGATCTGC

CGGGACTGCAGCCGGGTGCCGGGGGCACCCCGGGTGGCCCGGGCGGCGGCGGCGCTC
CCCCGCGCTACGCCACGCTGGAGCACCCCTTCCACTGCCCGCGCGTCCTCAAGGTGCCA
TCCTATCTCAGCTACAAGTTTCTGGGCGAGCGTGATTGTGCTGCGCCCTGCGAACCTGC
GCGGCCCGATGGTTCCATGTTCTTCTCACAGGAGGAGACGCGTTTCGCGCGCCTCTGGA
TCCTCACCTGGTCGGTGCTGTGCTGCGCTTCCACCTTCTTCACTGTCACCACGTACTTGG
TAGACATGCAGCGCTTCCGCTACCCAGAGCGGCCTATCATTTTTCTGTCGGGCTGCTAC
ACCATGGTGTCGGTGGCCTACATCGCGGGCTTCGTGCTCCAGGAGCGCGTGGTGTGCA
ACGAGCGCTTCTCCGAGGACGGTTACCGCACGGTGGTGCAGGGCACCAAGAAGGAGG
GCTGCACCATCCTCTTCATGATGCTCTACTTCTTCAGCATGGCCAGCTCCATCTGGTGG
GTCATCCTGTCGCTCACCTGGTTCCTGGCAGCCGGCATGAAGTGGGGCCACGAGGCCA
TCGAGGCCAACTCTCAGTACTTCCACCTGGCCGCCTGGGCCGTGCCGGCCGTCAAGAC
CATCACCATCCTGGCCATGGGCCAGATCGACGGCGACCTGCTGAGCGGCGTGTGCTTC
GTAGGCCTCAACAGCCTGGACCCGCTGCGGGGCTTCGTGCTAGCGCCGCTCTTCGTGTA
CCTGTTCATCGGCACGTCCTTCCTCCTGGCCGGCTTCGTGTCGCTCTTCCGCATCCGCAC
CATCATGAAGCACGACGGCACCAAGACCGAAAAGCTGGAGCGGCTCATGGTGCGCAT
CGGCGTCTTCTCCGTGCTCTACACAGTGCCCGCCACCATCGTCATCGCTTGCTACTTCTA
CGAGCAGGCCTTCCGCGAGCACTGGGAGCGCTCGTGGGTGAGCCAGCACTGCAAGAGC
CTGGCCATCCCGTGCCCGGCGCACTACACGCCGCGCATGTCGCCCGACTTCACGGTCTA
CATGATCAAATACCTCATGACGCTCATCGTGGGCATCACGTCGGGCTTCTGGATCTGGT
CGGGCAAGACGCTGCACTCGTGGAGGAAGTTCTACACTCGCCTCACCAACAGCCGACA
CGGTGAGACCACCGTGTGAGGGACGCCCCCAGGCCGGAACCGCGCGGCGCTTTCCTCC
GCCCGGGGTGGGGCCCCTACAGACTCCGTATTTATTTTTTTAAATAAAAAACGATCGA
AACCATTTCACTTTTAGGTTGCTTTTAAAAGAGAACTCTCTGCCCAACACCCCC

Figure 60

MRPRSALPRLLLPLLLLPAAGPAQFHGEKGISIPDHGFCQPISIPLCTDIAYNQTIMPNLLGHT
NQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCTVLEQAIPPCRSICERARQGCEALM
NKFGFQWPERLRCEHFPRHGAEQICVGQNHSEDGAPALLTTAPPPGLQPGAGGTPGGPGG
GGAPPRYATLEHPFHCPRVLKVPSYLSYKFLGERDCAAPCEPARPDGSMFFSQEETRFARL
WILTWSVLCCASTFFTVTTYLVDMQRFRYPERPIIFLSGCYTMVSVAYIAGFVLQERVVCN
ERFSEDGYRTVVQGTKKEGCTILFMMLYFFSMASSIWWVILSLTWFLAAGMKWGHEAIEA
NSQYFHLAAWAVPAVKTITILAMGQIDGDLLSGVCFVGLNSLDPLRGFVLAPLFVYLFIGTS
FLLAGFVSLFRIRTIMKHDGTKTEKLERLMVRIGVFSVLYTVPATIVIACYFYEQAFREHW
ERSWVSQHCKSLAIPCPAHYTPRMSPDFTVYMIKYLMTLIVGITSGFWIWSGKTLHSWRKF
YTRLTNSRHGETTV

Figure 61

GCCGCTCCGGGTACCTGAGGGACGCGCGGCCGCCCGCGGCAGGCGGTGCAGCCCCCCC
CCACCCCTTGGAGCCAGGCGCCGGGGTCTGAGGATAGCATTTCTCAAGACCTGACTTA
TGGAGCACTTGTAACCTGAGATATTTCAGTTGAAGGAAGAAATAGCTCTTCTCCTAAGA
TGGAATCTGTGGTTTGGGAATGTGGTTGATCAACTTGATATGTTGGCCAAATGTGCCCC
ATGTAATAAAATGAAAAGAAGAGACAAGATGATGTCATTTTCCCATATTGTGAAACCA
AAAACAAACGCCTTTTGTGAGACCAAGCTAACAAACCTCTGACGGTGCGAAGAGTATT
TAACTGTTTGAAGAATTTAACAGTAAGATACAGAAGAAGTACCTTCGAGCTGAGACCT
GCAGGTGTATAAATATCTAAAATACATATTGAATAGGCCTGATCATCTGAATCTCCTTC
AGACCCAGGAAGGATGGCTATGACTTGGATTGTCTTCTCTCTTTGGCCCTTGACTGTGT
TCATGGGGCATATAGGTGGCACAGTTTGTTTCTTGTGAACCTATTACCTTGAGGATG
TGCCAAGATTTGCCTTATAATACTACCTTCATGCCTAATCTTCTGAATCATTATGACCAA

GGATTTCCGGCCTTTTCTTTGTGCACTCTACGCTCCTATTTGTATGGAATATGGACGTGT
CACACTTCCCTGTCGTAGGCTGTGTCAGCGGGCTTACAGTGAGTGTTCGAAGCTCATGG
AGATGTTTGGTGTTCCTTGGCCTGAAGATATGGAATGCAGTAGGTTCCCAGATTGTGAT
GAGCCATATCCTCGACTTGTGGATCTGAATTTAGCTGGAGAACCAACTGAAGGAGCCC
CAGTGGCAGTGCAGAGAGACTATGGTTTTTGGTGTCCCCGAGAGTTAAAAATTGATCCT
GATCTGGGTTATTCTTTTCTGCATGTGCGTGATTGTTCACCTCCTTGTCCAAATATGTAC
TTCAGAAGAGAAGAACTGTCATTTGCTCGCTATTTCATAGGATTGATTTCAATCATTTG
CCTCTCGGCCACATTGTTTACTTTTTTAACTTTTTTGATTGATGTCACAAGATTCCGTTA
TCCTGAAAGGCCTATTATATTTTATGCAGTCTGCTACATGATGGTATCCTTAATTTTCTT
CATTGGATTTTTGCTTGAAGATCGAGTAGCCTGCAATGCATCCATCCCTGCACAATATA
AGGCTTCCACAGTGACACAAGGATCTCATAATAAAGCCTGTACCATGCTTTTTATGATA
CTCTATTTTTTTACTATGGCTGGCAGTGTATGGTGGGTAATTCTTACCATCACATGGTTT
TTAGCAGCTGTGCCAAAGTGGGGTAGTGAAGCTATTGAGAAGAAAGCATTGCTGTTTC
ACGCCAGTGCATGGGGCATCCCCGGAACTCTAACCATCATCCTTTTAGCGATGAATAA
AATTGAAGGTGACAATATTAGTGGCGTGTGTTTTGTTGGCCTCTACGATGTTGATGCAT
TGAGATATTTTGTTCTTGCTCCCCTCTGCCTGTATGTGGTAGTTGGGGTTTCTCTCCTCTT
AGCTGGCATTATATCCCTAAACAGAGTTCGAATTGAGATTCCATTAGAAAAGGAGAAC
CAAGATAAATTAGTGAAGTTTATGATCCGGATCGGTGTTTTCAGCATTCTTTATCTCGT
ACCACTCTTGGTTGTAATTGGATGCTACTTTTATGAGCAAGCTTACCGGGGCATCTGGG
AAACAACGTGGATACAAGAACGCTGCAGAGAATATCACATTCCATGTCCATATCAGGT
TACTCAAATGAGTCGTCCAGACTTGATTCTCTTTCTGATGAAATACCTGATGGCTCTCA
TAGTTGGCATTCCCTCTGTATTTTGGGTTGGAAGCAAAAAGACATGCTTTGAATGGGCC
AGTTTTTTTCATGGTCGTAGGAAAAAAGAGATAGTGAATGAGAGCCGACAGGTACTCC
AGGAACCTGATTTTGCTCAGTCTCTCCTGAGGGATCCAAATACTCCTATCATAAGAAAG
TCAAGGGGAACTTCCACTCAAGGAACATCCACCCATGCTTCTTCAACTCAGCTGGCTAT
GGTGGATGATCAAAGAAGCAAAGCAGGAAGCATCCACAGCAAAGTGAGCAGCTACCA
CGGCAGCCTCCACAGATCACGTGATGGCAGGTACACGCCCTGCAGTTACAGAGGAATG
GAGGAGAGACTACCTCATGGCAGCATGTCACGACTAACAGATCACTCCAGGCATAGTA
GTTCTCATCGGCTCAATGAACAGTCACGACATAGCAGCATCAGAGATCTCAGTAATAA
TCCCATGACTCATATCACACATGGCACCAGCATGAATCGGGTTATTGAAGAAGATGGA
ACCAGTGCTTAATTTGTCTTGTCTAAGGTGGAAATCTTGTGCTGTTTAAAAAGCAGATT
TTATTCTTTGCCTTTTGCATGACTGATAGCTGTACTCACAGTTAACATGCTTTCAGTCAA
GTACAGATTGTGTCCACTGGAAAGGTAAATGATTGCTTTTTTATATTGCATCAAACTTG
GAACATCAAGGCATCCAAAACACTAAGAATTCTATCATCACAAAAATAATTCGTCTTTC
TAGGTTATGAAGAGATAATTATTTGTCTGGTAAGCATTTTTATAAACCCACTCATTTTAT
ATTTAGAAAAATCCTAAATGTGTGGTGACTGCTTTGTAGTGAACTTTCATATACTATAA
ACTAGTTGTGAGATAACATTCTGGTAGCTCAGTTAATAAAACAATTTCAGAATTAAAG
AAATTTTCTATGCAAGGTTTACTTCTCAGATGAACAGTAGGACTTTGTAGTTTTATTTCC
ACTAAGTGAAAAAAGAACTGTGTTTTTAAACTGTAGGAGAATTTAATAAATCAGCAAG
GGTATTTTAGCTAATAGAATAAAAGTGCAACAGAAGAATTTGATTAGTCTATGAAAGG
TTCTCTTAAAATTCTATCGAAATAATCTTCATGCAGAGATATTCAGGGTTTGGATTAGC
AGTGGAATAAAGAGATGGGCATTGTTTCCCCTATAATTGTGCTGTTTTTATAACTTTTGT
AAATATTACTTTTTCTGGCTGTGTTTTTATAACTTATCCATATGCATGATGGAAAAATTT
TAATTTGTAGCCATCTTTTCCCATGTAATAGTATTGATTCATAGAGAACTTAATGTTCAA
AATTTGCTTTGTGGAGGCATGTAATAAGATAAACATCATACATTATAAGGTAACCACA
ATTACAAAATGGCAAAACA

Figure 62

MAMTWIVFSLWPLTVFMGHIGGHSLFSCEPITLRMCQDLPYNTTFMPNLLNHYDQQTAAL
[illegible]FLGALLHAPICMEYCRPVTLPCRPLCQRAYSECSKLMEMFGVP

WPEDMECSRFPDCDEPYPRLVDLNLAGEPTEGAPVAVQRDYGFWCPRELKIDPDLGYSFL
HVRDCSPPCPNMYFRREELSFARYFIGLISIICLSATLFTFLTFLIDVTRFRYPERPIIFYAVCY
MMVSLIFFIGFLLEDRVACNASIPAQYKASTVTQGSHNKACTMLFMILYFFTMAGSVWWVI
LTITWFLAAVPKWGSEAIEKKALLFHASAWGIPGTLTIILLAMNKIEGDNISGVCFVGLYDV
DALRYFVLAPLCLYVVVGVSLLLAGIISLNRVRIEIPLEKENQDKLVKFMIRIGVFSILYLVPL
LVVIGCYFYEQAYRGIWETTWIQERCREYHIPCPYQVTQMSRPDLILFLMKYLMALIVGIPS
VFWVGSKKTCFEWASFFHGRRKKEIVNESRQVLQEPDFAQSLLRDPNTPIIRKSRGTSTQGT
STHASSTQLAMVDDQRSKAGSIHSKVSSYHGSLHRSRDGRYTPCSYRGMEERLPHGSMSR
LTDHSRHSSSHRLNEQSRHSSIRDLSNNPMTHITHGTSMNRVIEEDGTSA

Figure 63

GCTGCGCAGCGCTGGCTGCTGGCTGGCCTCGCGGAGACGCCGAACGGACGCGGCCGGC
GCCGGCTTGTGGGCTCGCCGCCTGCAGCCATGACCCTCGCAGCCTGTCCCTCGGCCTCG
GCCCGGGACGTCTAAAATCCCACACAGTCGCGCGCAGCTGCTGGAGAGCCGGCCGCTG
CCCCCTCGTCGCCGCATCACACTCCCGTCCCGGGAGCTGGGAGCAGCGCGGGCAGCCG
GCGCCCCCGTGCAAACTGGGGGTGTCTGCCAGAGCAGCCCCAGCCGCTGCCGCTGCTA
CCCCCGATGCTGGCCATGGCCTGGCGGGGCGCAGGGCCGAGCGTCCCGGGGGCGCCCG
GGGGCGTCGGTCTCAGTCTGGGGTTGCTCCTGCAGTTGCTGCTGCTCCTGGGGCCGGCG
CGGGGCTTCGGGGACGAGGAAGAGCGGCGCTGCGACCCCATCCGCATCTCCATGTGCC
AGAACCTCGGCTACAACGTGACCAAGATGCCCAACCTGGTTGGGCACGAGCTGCAGAC
GGACGCCGAGCTGCAGCTGACAACTTTCACACCGCTCATCCAGTACGGCTGCTCCAGC
CAGCTGCAGTTCTTCCTTTGTTCTGTTTATGTGCCAATGTGCACAGAGAAGATCAACAT
CCCCATTGGCCCATGCGGCGGCATGTGTCTTTCAGTCAAGAGACGCTGTGAACCCGTCC
TGAAGGAATTTGGATTTGCCTGGCCAGAGAGTCTGAACTGCAGCAAATTCCCACCACA
GAACGACCACAACCACATGTGCATGGAAGGGCCAGGTGATGAAGAGGTGCCCTTACCT
CACAAAACCCCCATCCAGCCTGGGGAAGAGTGTCACTCTGTGGGAACCAATTCTGATC
AGTACATCTGGGTGAAAAGGAGCCTGAACTGTGTGCTCAAGTGTGGCTATGATGCTGG
CTTATACAGCCGCTCAGCCAAGGAGTTCACTGATATCTGGATGGCTGTGTGGGCCAGCC
TGTGTTTCATCTCCACTGCCTTCACAGTACTGACCTTCCTGATCGATTCTTCTAGGTTTT
CCTACCCTGAGCGCCCCATCATATTTCTCAGTATGTGCTATAATATTTATAGCATTGCTT
ATATTGTCAGGCTGACTGTAGGCCGGGAAAGGATATCCTGTGATTTTGAAGAGGCAGC
AGAACCTGTTCTCATCCAAGAAGGACTTAAGAACACAGGATGTGCAATAATTTTCTTGC
TGATGTACTTTTTTGGAATGGCCAGCTCCATTTGGTGGGTTATTCTGACACTCACTTGGT
TTTTGGCAGCAGGACTCAAATGGGGTCATGAAGCCATTGAAATGCACAGCTCTTATTTC
CACATTGCAGCCTGGGCCATCCCCGCAGTGAAAACCATTGTCATCTTGATTATGAGACT
GGTGGATGCAGATGAACTGACTGGCTTGTGCTATGTTGGAAACCAAAATCTCGATGCC
CTCACCGGGTTCGTGGTGGCTCCCCTCTTTACTTATTTGGTCATTGGAACTTTGTTCATT
GCTGCAGGTTTGGTGGCCTTGTTCAAAATTCGGTCAAATCTTCAAAAGGATGGGACAA
AGACAGACAAGTTAGAAAGACTGATGGTCAAGATTGGGGTGTTCTCAGTACTGTACAC
AGTTCCTGCAACGTGTGTGATTGCCTGTTATTTTTATGAAATCTCCAACTGGGCACTTTT
TCGGTATTCTGCAGATGATTCCAACATGGCTGTTGAAATGTTGAAAACTTTTATGTCTTT
GTTGGTGGGCATCACTTCAGGCATGTGGATTTGGTCTGCCAAAAGTCTTCACACGTGGC
AGAAGTGTTCCAACAGATTGGTGAATTCTGGAAAGGTAAAGAGAGAGAAGAGAGGAA
ATGGTTGGGTGAAGCCTGGAAAAGGCAGTGAGACTGTGGTATAAGGCTAGTCAGCCTC
CATGCTTTCTTCATTTTGAAGGGGGGAATGCCAGCATTTTGGAGGAAATTCTACTAAAA
GTTTTATGCAGTGAATCTCAGTTTGAACAAACTAGCAACAATTAAGTGACCCCCGTCAA
CCCACTGCCTCCCACCCCGACCCCAGCATCAAAAAACCAATGATTTTGCTGCAGACTTT
GGAATGATCCAAAATGGAAAAGCCAGTTAGAGGCTTTCAAAGCTGTGAAAAATCAAA
ACGTTGATCACTTTAGCAGGTTGCAGCTTGGAGCGTGGAGGTCCTGCCTAGATTCCAGG
AAGTCCAGGGCGATACTGTTTTCCCCTGCAGGGTGGGATTTGAGCTGTGAGTTGGTAAC

TTCAGATAGCAAAGCAATCTATAAACACTGGAAACGCTGGGTTCAGAAAAGTGTTACA
AGAGTTTTATAGTTTGGCTGATGTAACATAAACATCTTCTGTGGTGCGCTGTCTGCTGTT
TAGAACTTTGTGGACTGCACTCCCAAGAAGTGGTGTTAGAATCTTTCAGTGCCTTTGTC
ATAAAACAGTTATTTGAACAAACAAAAGTACTGTACTCACACACATAAGGTATCCAGT
GGATTTTTCTTCTCTGTCTTCCTCTCTTAAATTTCAACATCTCTCTTCTTGGCTGCTGCTG
TTTTCTTCATTTTATGTTAATGACTCAAAAAAGGTATTTTTATAGAATTTTTGTACTGCA
GCATGCTTAAAGAGGGGAAAAGGAAGGGTGATTCACTTTCTGACAATCACTTAATTCA
GAGGAAAATGAGATTTACTAAGTTGACTTACCTGACGGACCCCAGAGACCTATTGCAT
TGAGCAGTGGGGACTTAATATATTTTACTTGTGTGATTGCATCTATGCAGACGCCAGTC
TGGAAGAGCTGAAATGTTAAGTTTCTTGGCAACTTTGCATTCACACAGATTAGCTGTGT
AATTTTTGTGTGTCAATTACAATTAAAAGCACATTGTTGGACCATGACATAGTATACTC
AACTGACTTTAAAACTATGGTCAACTTCAACTTGCATTCTCAGAATGATAGTGCCTTTA
AAATTTTTTTATTTTTTAAAGCATAAGAATGTTATCAGAATCTGGTCTACTTAGGACAA
TGGAGACTTTTTCAGTTTTATAAAGGGAACTGAGGACAGCTAATCCAACTACTTGGTGC
TGTAATTGTTTCCTAGTAATTGGCAAAGGCTCCTTGTAAGATTTCACTGGAGGCAGTGT
GGCCTGGAGTATTTATATGGTGCTTAATGAATCTCCAGAATGCCAGCCAGAAGCCTGAT
TGGTTAGTAGGGAATAAAGTGTAGACCATATGAAATGAACTGCAAACTCTAATAGCCC
AGGTCTTAATTGCCTTTAGCAGAGGTATCCAAAGCTTTTAAAATTTATGCATACGTTCT
TCACAAGGGGGTACCCCCAGCAGCCTCTCGAAAATTGCACTTCTCTTAAAACTGTAACT
GGCCTTTCTCTTACCTTGCCTTAGGCCTTCTAATCATGAGATCTTGGGGACAAATTGACT
ATGTCACAGGTTGCTCTCCTTGTAACTCATACCTGTCTGCTTCAGCAACTGCTTTGCAAT
GACATTTATTTATTAATTCATGCCTTAAAAAAATAGGAAGGGAAGCTTTTTTTTTTCTTT
TTTTTTTTTCAATCACACTTTGTGGAAAAACATTTCCAGGGACTCAAAATTCCAAAAA
GGTGGTCAAATTCTGGAAGTAAGCATTTCCTCTTTTTTAAAAATTTGGTTTGAGCCTTAT
GCCCATAGTTTGACATTTCCCTTTCTTCTTTCCTTTTTGTTTTTGTGTGGTTCTTGAGCTC
TCTGACATCAAGATGCATGTAAAGTCGATTGTATGTTTTGAAGGCAAAGTCTTGGCTTT
TGAGACTGAAGTTAAGTGGGCACAGGTGGCCCCTGCTGCTGTGCCCAGTCTGAGTACC
TTGGCTAGACTCTAGGTCAGGCTCCAGGAGCATGAGAATTGATCCCCAGAAGAACCAT
TTTAACTCCATCTGATACTCCATTGCCTATGAAATGTAAAATGTGAACTCCCTGTGCTG
CTTGTAGACAGTTCCCATAACTGTCCACGGCCCTGGAGCACGCACCCAGGGGCAGAGC
CTGCCCTTACTCACGCTCTGCTCTGGTGTCTTGGGAGTTGTGCAGGGACTCTGGCCCAG
GCAGGGGAAGGAAGACCAGGCGGTAGGGGACTGGTCTTGCTGTTAGAGTATAGAGGTT
TGTAATGCAGTTTTCTTCATAATGTGTCAGTGATTGTGTGACCAAGGCAGCATCTAGCA
GAAAGCCAGGCATGGAGTAGGTGATCGATACTTGTCAATGACTAAATAATAACAATAA
AAGAGCACTTGGGTGAATCTGGGCACCTGATTTCTGAGTTTTGAGTTCTGGAGCTAGTG
TTTTGACAATGCTTTGGGTTTTGACATGCCTTTTCCACAAATCTCTTGCCTTTTCAGGGC
AAAGTGTATTTGATCAGAAGTGGCCATTTGGATTAGTAGCCTTAGCAATGCTACAGGGT
TATAGGCCCCTCTCCCTTTCACATTCCAGACAATGGAGAGTGTTTATGGTTTCAGGAAA
AGAACTTTGTGGCTGAGGGGTCAGTTACCAGTGACCTTCAATCAACTCCATCACTTCTT
AAATCGGTATTTGTTAAAAAAATCAGTTATTTTATTTATTGAGTGCCGACTGTAGTAAA
GCCCTGAAATAGATAATCTCTGTTCTTCTAACTGATCTAGGATGGGGACGCACCCAGGT
CTGCTGAACTTTACTGTTCCTCTGGGAAAGGAGCAGGGACCTCTGGAATTCCCATCTGT
TTCACTGTCTCCATTCCATAAATCTCTTCCTGTGTGAGCCACCACACCCAGCCTGGGTCT
CTCTACTTTTAACACATCTCTCATCCCTTTCCCAGGACTTCCTTCCAAGTCAGTTACAGG
TGGTTTTAACAGAAAGCATCAGCTCTGCTTCGTGACAGTCTCTGGAGAAATCCCTTAGG
AAGACTATGAGAGTAGGCCACAAGGACATGGGCCCACACATCTGCTTTGGCTTTGCCG
GCAATTCAGGGCTTGGGGTATTCCATGTGACTTGTATAGGTATATTTGAGGACAGCATC
TTGCTAGAGAAAAGGTGAGGGTTGTTTTTCTTTCTCTGAAACCTACAGTAAATGGGTAT
GATTGTAGCTTCCTCAGAAATCCCTTGGCCTCCAGAGATTAAACATGGTGCAATGGCAC
CTCTGTCCAACCTCCTTTCTGGTAGATTCCTTTCTCCTGCTTCATATAGGCCAAACCTCA
GGGCAAGGGAACATGGGGGTAGAGTGGTGCTGGCCAGAACCATCTGCTTGAGCTACTT
[illegible]ATGGAGACCCATTTCCTGATCTCTGAGACTGTTGC

TGAACTGGCAACTTACTTGGGCCTGAAACTGGAGAAGGGGTGACATTTTTTAATTTCA
GAGATGCTTTCTGATTTCCTCTCCCAGGTCACTGTCTCACCTGCACTCTCCAAACTCAG
GTTCCGGGAAGCTTGTGTGTCTAGATACTGAATTGAGATTCTGTTCAGCACCTTTTAGC
TCTATACTCTCTGGCTCCCCTCATCCTCATGGTCACTGAATTAAATGCTTATTGTATTGA
GAACCAAGATGGGACCTGAGGACACAAAGATGAGCTCAACAGTCTCAGCCCTAGAGG
AATAGACTCAGGGATTTCACCAGGTCGGTGCAGTATTTGATTTCTGGTGAGGTGACCAC
AGCTGCAGTTAGGAAGGGAGCCATTGAGCACAGACTTTGGAAGGAACCTTTTTTTGTT
GTTTGTTTGTTTGTTTGTTTGTTTGTTTGTTTGAGACAGGGTCTTGCTCTGCTACCCAGG
CTGGGGCGCAATGGCACGATCTTGGCTCACTGCAACCTCTGCCTCCTGGGTTCAAGTGA
TTCTCCTGCCACAGCCTCCTGAGGAGCTGGGACTACAGGTGCGTGCTACCACGCCCAG
CTACTTCTGTATTTTTAGTAGAGACGGGGTTTCACTGTGTTGGCCAGGCTGGTCTCGAA
CTCCTGACCTCATGATCTGCCCGCCTCAGCCTCCCAAAGTGCTGGGATTACAAGTGTGA
GCCACCACACCTGGCCTGGAAGGAACCTCTTAAAATCAGTTTACGTCTTGTATTTTGTT
CTGTGATGGAGGACACTGGAGAGAGTTGCTATTCCAGTCAATCATGTCGAGTCACTGG
ACTCTGAAAATCCTATTGGTTCCTTTATTTATTTGAGTTTAGAGTTCCCTTCTGGGTTT
GTATTATGTCTGGCAAATGACCTGGGTTATCACTTTTCCTCCAGGGTTAGATCATAGAT
CTTGGAAACTCCTTAGAGAGCATTTTGCTCCTACCAAGGATCAGATACTGGAGCCCCAC
ATAATAGATTTCATTTCACTCTAGCCTACATAGAGCTTTCTGTTGCTGTCTCTTGCCATG
CACTTGTGCGGTGATTACACACTTGACAGTACCAGGAGACAAATGACTTACAGATCCC
CCGACATGCCTCTTCCCCTTGGCAAGCTCAGTTGCCCTGATAGTAGCATGTTTCTGTTTC
TGATGTACCTTTTTTCTCTTCTTCTTTGCATCAGCCAATTCCCAGAATTTCCCCAGGCAA
TTTGTAGAGGACCTTTTTGGGGTCCTATATGAGCCATGTCCTCAAAGCTTTTAAACCTC
CTTGCTCTCCTACAATATTCAGTACATGACCACTGTCATCCTAGAAGGCTTCTGAAAAG
AGGGGCAAGAGCCACTCTGCGCCACAAAGGTTGGATCCATCTTCTCTCCGAGGTTGTG
AAAGTTTTCAAATTGTACTAATAGGCTGGGGCCCTGACTTGGCTGTGGGCTTTGGGAGG
GGTAAGCTGCTTTCTAGATCTCTCCCAGTGAGGCATGGAGGTGTTTCTGAATTTTGTCT
ACCTCACAGGGATGTTGTGAGGCTTGAAAAGGTCAAAAAATGATGGCCCCTTGAGCTC
TTTGTAAGAAAGGTAGATGAAATATCGGATGTAATCTGAAAAAAAGATAAAATGTGAC
TTCCCCTGCTCTGTGCAGCAGTCGGGCTGGATGCTCTGTGGCNTTTCTTGGGTCCTCATG
CCACCCCACAGCTCCAGGAACCTTGAAGCCAATCTGGGGACTTTCAGATGTTTGACAA
AGAGGTACCAGGCAAACTTCCTGCTACACATGCCCTGAATGAATTGCTAAATTTCAAA
GGAAATGGACCCTGCTTTTAAGGATGTACAAAAGTATGTCTGCATCGATGTCTGTACTG
TAAATTTCTAATTTATCACTGTACAAAGAAAACCCCTTGCTATTTAATTTTGTATTAAAG
GAAAATAAAGTTTTGTTTGTTAAAAAAAAA

Figure 64

MAWRGAGPSVPGAPGGVGLSLGLLLQLLLLLGPARGFGDEEERRCDPIRISMCQNLGYNV
TKMPNLVGHELQTDAELQLTTFTPLIQYGCSSQLQFFLCSVYVPMCTEKINIPIGPCGGMCL
SVKRRCEPVLKEFGFAWPESLNCSKFPPQNDHNHMCMEGPGDEEVPLPHKTPIQPGEECHS
VGTNSDQYIWVKRSLNCVLKCGYDAGLYSRSAKEFTDIWMAVWASLCFISTAFTVLTFLID
SSRFSYPERPIIFLSMCYNIYSIAYIVRLTVGRERISCDFEEAAEPVLIQEGLKNTGCAIIFLLM
YFFGMASSIWWVILTLTWFLAAGLKWGHEAIEMHSSYFHIAAWAIPAVKTIVILIMRLVDA
DELTGLCYVGNQNLDALTGFVVAPLFTYLVIGTLFIAAGLVALFKIRSNLQKDGTKTDKLE
RLMVKIGVFSVLYTVPATCVIACYFYEISNWALFRYSADDSNMAVEMLKTFMSLLVGIT
SGMWIWSAKSLHTWQKCSNRLVNSGKVKREKRGNGWVKPGKGSETVV

Figure 65

ACCCAGGGACGGAGGACCCAGGCTGGCTTGGGGACTGTCTGCTCTTCTCGGCGGGAGC
CGTGGAGAGTCCTTTCCCTGGAATCCGAGCCCTAACCGTCTCTCCCCAGCCCTATCCGG
CGAGGAGCGGAGCGCTGCCAGCGGAGGCAGCGCCTTCCCGAAGCAGTTTATCTTTGGA
CGGTTTTCTTTAAAGGAAAAACGAACCAACAGGTTGCCAGCCCCGGCGCCACACACGA
GACGCCGGAGGGAGAAGCCCCGGCCCGGATTCCTCTGCCTGTGTGCGTCCCTCGCGGG
CTGCTGGAGGCGAGGGGAGGGAGGGGGCGATGGCTCGGCCTGACCCATCCGCGCCGC
CCTCGCTGTTGCTGCTGCTCCTGGCGCAGCTGGTGGGCCGGGCGGCCGCCGCGTCCAA
GGCCCCGGTGTGCCAGGAAATCACGGTGCCCATGTGCCGCGGCATCGGCTACAACCTG
ACGCACATGCCCAACCAGTTCAACCACGACACGCAGGACGAGGCGGGCCTGGAGGTG
CACCAGTTCTGGCCGCTGGTGGAGATCCAATGCTCGCCGGACCTGCGCTTCTTCCTATG
CACTATGTACACGCCCATCTGTCTGCCCGACTACCACAAGCCGCTGCCGCCCTGCCGCT
CGGTGTGCGAGCGCGCCAAGGCCGGCTGCTCGCCGCTGATGCGCCAGTACGGCTTCGC
CTGGCCCGAGCGCATGAGCTGCGACCGCCTCCCGGTGCTGGGCCGCGACGCCGAGGTC
CTCTGCATGGATTACAACCGCAGCGAGGCCACCACGGCGCCCCCCAGGCCTTTCCCAG
CCAAGCCCACCCTTCCAGGCCCGCCAGGGGCGCCGGCCTCGGGGGGCGAATGCCCCGC
TGGGGGCCCGTTCGTGTGCAAGTGTCGCGAGCCCTTCGTGCCCATTCTGAAGGAGTCAC
ACCCGCTCTACAACAAGGTGCGGACGGGCCAGGTGCCCAACTGCGCGGTACCCTGCTA
CCAGCCGTCCTTCAGTGCCGACGAGCGCACGTTCGCCACCTTCTGGATAGGCCTGTGGT
CGGTGCTGTGCTTCATCTCCACGTCCACCACAGTGGCCACCTTCCTCATCGACATGGAC
ACGTTCCGCTATCCTGAGCGCCCCATCATCTTCCTGTCAGCCTGCTACCTGTGCGTGTC
GCTGGGCTTCCTGGTGCGTCTGGTCGTGGGCCATGCCAGCGTGGCCTGCAGCCGCGAG
CACAACCACATCCACTACGAGACCACGGGCCCTGCACTGTGCACCATCGTCTTCCTCCT
GGTCTACTTCTTCGGCATGGCCAGCTCCATCTGGTGGGTCATCCTGTCGCTCACCTGGTT
CCTGGCCGCCGCGATGAAGTGGGGCAACGAGGCCATCGCGGGCTACGGCCAGTACTTC
CACCTGGCTGCGTGGCTCATCCCCAGCGTCAAGTCCATCACGGCACTGGCGCTGAGCTC
CGTGGACGGGGACCCAGTGGCCGGCATCTGCTACGTGGGCAACCAGAACCTGAACTCG
CTGCGGCGCTTCGTGCTGGGCCCGCTGGTGCTCTACCTGCTGGTGGGCACGCTCTTCCT
GCTGGCGGGCTTCGTGTCGCTCTTCCGCATCCGCAGCGTCATCAAGCAGGGCGGCACC
AAGACGGACAAGCTGGAGAAGCTCATGATCCGCATCGGCATCTTCACGCTGCTCTACA
CGGTCCCCGCCAGCATTGTGGTGGCCTGCTACCTGTACGAGCAGCACTACCGCGAGAG
CTGGGAGGCGGCGCTCACCTGCGCCTGCCCGGGCCACGACACCGGCCAGCCGCGCGCC
AAGCCCGAGTACTGGGTGCTCATGCTCAAGTACTTCATGTGCCTGGTGGTGGGCATCAC
GTCGGGCGTCTGGATCTGGTCGGGCAAGACGGTGGAGTCGTGGCGGCGTTTCACCAGC
CGCTGCTGCTGCCGCCCGCGGCGCGGCCACAAGAGCGGGGGCGCCATGGCCGCAGGG
GACTACCCCGAGGCGAGCGCCGCGCTCACAGGCAGGACCGGGCCGCCGGGCCCCGCC
GCCACCTACCACAAGCAGGTGTCCCTGTCGCACGTGTAGGAGGCTGCCGCCGAGGGAC
TCGGCCGGAGAGCTGAGGGGAGGGGGGCGTTTTGTTTGGTAGTTTTGCCAAGGTCACT
TCCGTTTACCTTCATGGTGCTGTTGCCCCCTCCCGCGGCGACTTGGAGAGAGGGAAGAG
GGGCGTTTTCGAGGAAGAACCTGTCCCAGGTCTTCTCCAAGGGGCCCAGCTCACGTGT
ATTCTATTTTGCGTTTCTTACCTGCCTTCTTTATGGGAACCCTCTTTTTAATTTATATGTA
T

Figure 66

MARPDPSAPPSLLLLLLAQLVGRAAAASKAPVCQEITVPMCRGIGYNLTHMPNQFNHDTQ
DEAGLEVHQFWPLVEIQCSPDLRFFLCTMYTPICLPDYHKPLPPCRSVCERAKAGCSPLMR
QYGFAWPERMSCDRLPVLGRDAEVLCMDYNRSEATTAPPRPFPAKPTLPGPPGAPASGGE
CPAGGPFVCKCREPFVPILKESHPLYNKVRTGQVPNCAVPCYQPSFSADERTFATFWIGLW
SVLCFISTSTTVATFLIDMDTFRYPERPIIFLSACYLCVSLGFLVRLVVGHASVACSREHNHIH
YETTGPALCTIVFLLVYFFGMASSIWWVILSLTWFLAAAMKWGNEAIAGYGQYFHLAAWL
IPSVKSITALALSSVDGDPVAGICYVGNQNLNSLRRFVLGPLVLYLLVGTLFLLAGFVSLFRI
RSVIKQGGTKTDKLEKLMIRIGIFTLLYTVPASIVVACYLYEQHYRESWEAALTCACPGHD
TGQPRAKPEYWVLMLKYFMCLVVGITSGVWIWSGKTVESWRRFTSRCCCRPRRGHKSGG
AMAAGDYPEASAALTGRTGPPGPAATYHKQVSLSHV

Figure 67

GCAGCTCCAGTCCCGGACGCAACCCCGGAGCCGTCTCAGGTCCCTGGGGGGAACGGTG
GGTTAGACGGGGACGGGAAGGGACAGCGGCCTTCGACCGCCCCCCGAGTAATTGACCC
AGGACTCATTTTCAGGAAAGCCTGAAAATGAGTAAAATAGTGAAATGAGGAATTTGAA
CATTTTATCTTTGGATGGGGATCTTCTGAGGATGCAAAGAGTGATTCATCCAAGCCATG
TGGTAAAATCAGGAATTTGAAGAAAATGGAGATGTTTACATTTTTGTTGACGTGTATTT
TTCTACCCCTCCTAAGAGGGCACAGTCTCTTCACCTGTGAACCAATTACTGTTCCCAGA
TGTATGAAAATGGCCTACAACATGACGTTTTTCCCTAATCTGATGGGTCATTATGACCA
GAGTATTGCCGCGGTGGAAATGGAGCATTTTCTTCCTCTCGCAAATCTGGAATGTTCAC
CAAACATTGAAACTTTCCTCTGCAAAGCATTTGTACCAACCTGCATAGAACAAATTCAT
GTGGTTCCACCTTGTCGTAAACTTTGTGAGAAAGTATATTCTGATTGCAAAAAATTAAT
TGACACTTTTGGGATCCGATGGCCTGAGGAGCTTGAATGTGACAGATTACAATACTGTG
ATGAGACTGTTCCTGTAACTTTTGATCCACACACAGAATTTCTTGGTCCTCAGAAGAAA
ACAGAACAAGTCCAAAGAGACATTGGATTTTGGTGTCCAAGGCATCTTAAGACTTCTG
GGGGACAAGGATATAAGTTTCTGGGAATTGACCAGTGTGCGCCTCCATGCCCCAACAT
GTATTTTAAAAGTGATGAGCTAGAGTTTGCAAAAAGTTTTATTGGAACAGTTTCAATAT
TTTGTCTTTGTGCAACTCTGTTCACATTCCTTACTTTTTTAATTGATGTTAGAAGATTCA
GATACCCAGAGAGACCAATTATATATTACTCTGTCTGTTACAGCATTGTATCTCTTATG
TACTTCATTGGATTTTTGCTGGGCGATAGCACAGCCTGCAATAAGGCAGATGAGAAGC
TAGAACTTGGTGACACTGTTGTCCTAGGCTCTCAAAATAAGGCTTGCACCGTTTTGTTC
ATGCTTTTGTATTTTTTCACAATGGCTGGCACTGTGTGGTGGGTGATTCTTACCATTACT
TGGTTCTTAGCTGCAGGAAGAAAATGGAGTTGTGAAGCCATCGAGCAAAAAGCAGTGT
GGTTTCATGCTGTTGCATGGGGAACACCAGGTTTCCTGACTGTTATGCTTCTTGCTCTGA
ACAAAGTTGAAGGAGACAACATTAGTGGAGTTTGCTTTGTTGGCCTTTATGACCTGGAT
GCTTCTCGCTACTTTGTACTCTTGCCACTGTGCCTTTGTGTGTTTGTTGGGCTCTCTCTTC
TTTTAGCTGGCATTATTTCCTTAAATCATGTTCGACAAGTCATACAACATGATGGCCGG
AACCAAGAAAAACTAAAGAAATTTATGATTCGAATTGGAGTCTTCAGCGGCTTGTATC
TTGTGCCATTAGTGACACTTCTCGGATGTTACGTCTATGAGCAAGTGAACAGGATTACC
TGGGAGATAACTTGGGTCTCTGATCATTGTCGTCAGTACCATATCCCATGTCCTTATCA
GGCAAAAGCAAAAGCTCGACCAGAATTGGCTTTATTTATGATAAAATACCTGATGACA
TTAATTGTTGGCATCTCTGCTGTCTTCTGGGTTGGAAGCAAAAAGACATGCACAGAATG
GGCTGGGTTTTTTAAACGAAATCGCAAGAGAGATCCAATCAGTGAAAGTCGAAGAGTA
CTACAGGAATCATGTGAGTTTTTCTTAAAGCACAATTCTAAAGTTAAACACAAAAAGA
AGCACTATAAACCAAGTTCACACAAGCTGAAGGTCATTTCCAAATCCATGGGAACCAG
CACAGGAGCTACAGCAAATCATGGCACTTCTGCAGTAGCAATTACTAGCCATGATTAC
CTAGGACAAGAAACTTTGACAGAAATCCAAACCTCACCAGAAACATCAATGAGAGAG
GTGAAAGCGGACGGAGCTAGCACCCCCAGGTTAAGAGAACAGGACTGTGGTGAACCT
GCCTCGCCAGCAGCATCCATCTCCAGACTCTCTGGGGAACAGGTCGACGGGAAGGGCC
AGGGAGGGACTCTATCTGAAAGTGCGCGGAGTGAAGGAAGGATTAGTCCAAAGAGTG

ATATTACTGACACTGGCCTGGCACAGAGCAACAATTTGCAGGTCCCCAGTTCTTCAGAA
CCAAGCAGCCTCAAAGGTTCCACATCTCTGCTTGTTCACCCAGTTTCAGGAGTGAGAAA
AGAGCAGGGAGGTGGTTGTCATTCAGATACTTGAAGAACATTTTCTCTCGTTACTCAGA
AGCAAATTTGTGTTACACTGGAAGTGACCTATGCACTGTTTTGTAAGAATCACTGTTAC
GTTCTTCTTTTGCACTTAAAGTTGCATTGCCTACTGTTATACTGGAAAAAATAGAGTTC
AAGAATAATATGACTCATTTCACACAAAGGTTAATGACAACAATATACCTGAAAACAG
AAATGTGCAGGTTAATAATATTTTTTTAATAGTGTGGGAGGACAGAGTTAGAGGAATC
TTCCTTTTCTATTTATGAAGATTCTACTCTTGGTAAGAGTATTTTAAGATGTACTATGCT
ATTTTACCTTTTTGATATAAAATCAAGATATTTCTTTGCTGAAGTATTTAAATCTTATCC
TTGTATCTTTTTATACATATTTGAAAATAAGCTTATATGTATTTGAACTTTTTTGAAATC
CTATTCAAGTATTTTTATCATGCTATTGTGATATTTTAGCACTTTGGTAGCTTTTACACT
GAATTTCTAAGAAAATTGTAAAATAGTCTTCTTTTATACTGTAAAAAAAGATATACCAA
AAAGTCTTATAATAGGAATTTAACTTTAAAAACCCACTTATTGATACCTTACCATCTAA
AATGTGTGATTTTTATAGTCTCGTTTTAGGAATTTCACAGATCTAAATTATGTAACTGA
AATAAGGTGCTTACTCAAAGAGTGTCCACTATTGATTGTATTATGCTGCTCACTGATCC
TTCTGCATATTTAAAATAAAATGTCCTAAAGGGTTAGTAGACAAAATGTTAGTCTTTTG
TATATTAGGCCAAGTGCAATTGACTTCCCTTTTTTAATGTTTCATGACCACCCATTGATT
GTATTATAACCACTTACAGTTGCTTATATTTTTTGTTTTAACTTTTGTTTCTTAACATTTA
GAATATTACATTTTGTATTATACAGTACCTTTCTCAGACATTTTGTAG

Figure 68

MEMFTFLLTCIFLPLLRGHSLFTCEPITVPRCMKMAYNMTFFPNLMGHYDQSIAAVEMEHF
LPLANLECSPNIETFLCKAFVPTCIEQIHVVPPCRKLCEKVYSDCKKLIDTFGIRWPEELECD
RLQYCDETVPVTFDPHTEFLGPQKKTEQVQRDIGFWCPRHLKTSGGQGYKFLGIDQCAPPC
PNMYFKSDELEFAKSFIGTVSIFCLCATLFTFLTFLIDVRRFRYPERPIIYYSVCYSIVSLMYFI
GFLLGDSTACNKADEKLELGDTVVLGSQNKACTVLFMLLYFFTMAGTVWWVILTITWFLA
AGRKWSCEAIEQKAVWFHAVAWGTPGFLTVMLLALNKVEGDNISGVCFVGLYDLDASRY
FVLLPLCLCVFVGLSLLLAGIISLNHVRQVIQHDGRNQEKLKKFMIRIGVFSGLYLVPLVTLL
GCYVVYEQVNRITWEITWVSDHCRQYHIPCPYQAKAKARPELALFMIKYLMTLIVGISA
VFWVGSKKTCTEWAGFFKRNRKRDPISESRRVLQESCEFFLKHNSKVKHKKKHYKPSSHK
LKVISKSMGTSTGATANHGTSAVAITSHDYLGQETLTEIQTSPETSMREVKADGASTPRLRE
QDCGEPASPAASISRLSGEQVDGKGQAGSVSESARSEGRISPKSDITDTGLAQSNNLQVPSSS
EPSSLKGSTSLLVHPVSGVRKEQGGGCHSDT

Figure 69

CTCTCCCAACCGCCTCGTCGCACTCCTCAGGCTGAGAGCACCGCTGCACTCGCGGCCGG
CGATGCGGGACCCCGGCGCGGCCGCTCCGCTTTCGTCCCTGGGCCTCTGTGCCCTGGTG
CTGGCGCTGCTGGGCGCACTGTCCGCGGGCGCCGGGGCGCAGCCGTACCACGGAGAGA
AGGGCATCTCCGTGCCGGACCACGGCTTCTGCCAGCCCATCTCCATCCCGCTGTGCACG
GACATCGCCTACAACCAGACCATCCTGCCCAACCTGCTGGGCCACACGAACCAAGAGG
ACGCGGGCCTCGAGGTGCACCAGTTCTACCCGCTGGTGAAGGTGCAGTGTTCTCCCGA
ACTCCGCTTTTTCTTATGCTCCATGTATGCGCCCGTGTGCACCGTGCTCGATCAGGCCAT
CCCGCCGTGTCGTTCTCTGTGCGAGCGCGCCCGCCAGGGCTGCGAGGCGCTCATGAAC
AAGTTCGGCTTCCAGTGGCCCGAGCGGCTGCGCTGCGAGAACTTCCCGGTGCACGGTG
CGGGCGAGATCTGCGTGGGCCAGAACACGTCGGACGGCTCCGGGGGCCCAGGCGGCG
GCCCCACTGCCTACCCTACCGCGCCCTACCTGCCGGACCTGCCCTTCACCGCGCTGCCC

CAAGGTGCCCCCGTACCTGGGCTACCGCTTCCTGGGTGAGCGCGATTGTGGCGCCCCGT
GCGAACCGGGCCGTGCCAACGGCCTGATGTACTTTAAGGAGGAGGAGAGGCGCTTCGC
CCGCCTCTGGGTGGGCGTGTGGTCCGTGCTGTGCTGCGCCTCGACGCTCTTTACCGTTC
TCACCTACCTGGTGGACATGCGGCGCTTCAGCTACCCAGAGCGGCCCATCATCTTCCTG
TCGGGCTGCTACTTCATGGTGGCCGTGGCGCACGTGGCCGGCTTCCTTCTAGAGGACCG
CGCCGTGTGCGTGGAGCGCTTCTCGGACGATGGCTACCGCACGGTGGCGCAGGGCACC
AAGAAGGAGGGCTGCACCATCCTCTTCATGGTGCTCTACTTCTTCGGCATGGCCAGCTC
CATCTGGTGGGTCATTCTGTCTCTCACTTGGTTCCTGGCGGCCGGCATGAAGTGGGGCC
ACGAGGCCATCGAGGCCAACTCGCAGTACTTCCACCTGGCCGCGTGGGCCGTGCCCGC
CGTCAAGACCATCACTATCCTGGCCATGGGCCAGGTAGACGGGGACCTGCTGAGCGGG
GTGTGCTACGTTGGCCTCTCCAGTGTGGACGCGCTGCGGGGCTTCGTGCTGGCGCCTCT
GTTCGTCTACCTCTTCATAGGCACGTCCTTCTTGCTGGCCGGCTTCGTGTCCCTCTTCCG
TATCCGCACCATCATGAAACACGACGGCACCAAGACCGAGAAGCTGGAGAAGCTCAT
GGTGCGCATCGGCGTCTTCAGCGTGCTCTACACAGTGCCCGCCACCATCGTCCTGGCCT
GCTACTTCTACGAGCAGGCCTTCCGCGAGCACTGGGAGCGCACCTGGCTCCTGCAGAC
GTGCAAGAGCTATGCCGTGCCCTGCCCGCCCGGCCACTTCCCGCCCATGAGCCCCGACT
TCACCGTCTTCATGATCAAGTACCTGATGACCATGATCGTCGGCATCACCACTGGCTTC
TGGATCTGGTCGGGCAAGACCCTGCAGTCGTGGCGCCGCTTCTACCACAGACTTAGCC
ACAGCAGCAAGGGGGAGACTGCGGTATGAGCCCCGGCCCCTCCCCACCTTTCCCACCC
CAGCCCTCTTGCAAGAGGAGAGGCACGGTAGGGAAAAGAACTGCTGGGTGGGGGCCT
GTTTCTGTAACTTTCTCCCCCTCTACTGAGAAGTGACCTGGAAGTGAGAAGTTCTTTGC
AGATTTGGGGCGAGGGGTGATTTGGAAAAGAAGACCTGGGTGGAAAGCGGTTTGGAT
GAAAAGATTTCAGGCAAAGACTTGCAGGAAGATGATGATAACGGCGATGTGAATCGTC
AAAGGTACGGGCCAGCTTGTGCCTAATAGAAGGTTGAGACCAGCAGAGACTGCTGTGA
GTTTCTCCCGGCTCCGAGGCTGAACGGGGACTGTGAGCGATCCCCCTGCTGCAGGGCG
AGTGGCCTGTCCAGACCCCTGTGAGGCCCCGGGAAAGGTACAGCCCTGTCTGCGGTGG
CTGCTTTGTTGGAAAGAGGGAGGGCCTCCTGCGGTGTGCTTGTCAAGCAGTGGTCAAA
CCATAATCTCTTTTCACTGGGGCCAAACTGGAGCCCAGATGGGTTAATTTCCAGGGTCA
GACATTACGGTCTCTCCTCCCCTGCCCCCTCCCGCCTGTTTTTCCTCCCGTACTGCTTTC
AGGTCTTGTAAAATAAGCATTTGGAAGTCTTGGGAGGCCTGCCTGCTAGAATCCTAATG
TGAGGATGCAAAAGAAATGATGATAACATTTTGAGATAAGGCCAAGGAGACGTGGAG
TAGGTATTTTTGCTACTTTTTCATTTTCTGGGGAAGGCAGGAGGCAGAAAGACGGGTGT
TTTATTTGGTCTAATACCCTGAAAAGAAGTGATGACTTGTTGCTTTTCAAAACAGGAAT
GCATTTTTCCCCTTGTCTTTGTTGTAAGAGACAAAAGAGGAAACAAAAGTGTCTCCCTG
TGGAAAGGCATAACTGTGACGAAAGCAACTTTTATAGGCAAAGCAGCGCAAATCTGAG
GTTTCCCGTTGGTTGTTAATTTGGTTGAGATAAACATTCCTTTTTAAGGAAAAGTGAAG
AGCAGTGTGCTGTCACACACCGTTAAGCCAGAGGTTCTGACTTCGCTAAAGGAAATGT
AAGAGGTTTTGTTGTCTGTTTTAAATAAATTTAATTCGGAACACATGATCCAACAGACT
ATGTTAAAATATTCAGGGAAATCTCTCCCTTCATTTACTTTTTCTTGCTATAAGCCTATA
TTTAGGTTTCTTTTCTATTTTTTTCTCCCATTTGGATCCTTTGAGGTAAAAAAACATAAT
GTCTTCAGCCTCATAATAAAGGAAAGTTAATTAAAAAAAAAAAGCAAAGAGCCATTTT
GTCCTGTTTTCTTGGTTCCATCAATCTGTTTATTAAACATCATCCATATGCTGACCCTGT
CTCTGTGTGGTTGGGTTGGGAGGCGATCAGCAGATACCATAGTGAACGAAGAGGAAGG
TTTGAACCATGGGCCCCATCTTTAAAGAAAGTCATTAAAAGAAGGTAAACTTCAAAGT
GATTCTGGAGTTCTTTGAAATGTGCTGGAAGACTTAAATTTATTAATCTTAAATCATGT
ACTTTTTTTCTGTAATAGAACTCGGATTCTTTTGCATGATGGGGTAAAGCTTAGCAGAG
AATCATGGGAGCTAACCTTTATCCCACCTTTGACACTACCCTCCAATCTTGCAACACTA
TCCTGTTTCTCAGAACAGTTTTTAAATGCCAATCATAGAGGGTACTGTAAAGTGTACAA
GTTACTTTATATATGTAATGTTCACTTGAGTGGAACTGCTTTTTACATTAAAGTTAAAAT
CGATCTTGTGTTTCTTCAACCTTCAAAACTATCTCATCTGTCAGATTTTTAAAACTCCAA
CACAGGTTTTGGCATCTTTTGTGCTGTATCTTTTAAGTGCATGTGAAATTTGTAAAATAG
[illegible]CTATATTTTCTAAATCTGCCATTTTTGTAAGAAAATATATATTG

TATTTATACATTTTTACTTTGGATTTTTGTTTTGTTGGCTTTAAAGGTCTACCCCACTTTA
TCACATGTACAGATCACAAATAAATTTTTTTAAATAC

Figure 70

MRDPGAAAPLSSLGLCALVLALLGALSAGAGAQPYHGEKGISVPDHGFCQPISIPLCTDIAY
NQTILPNLLGHTNQEDAGLEVHQFYPLVKVQCSPELRFFLCSMYAPVCTVLDQAIPPCRSLC
ERARQGCEALMNKFGFQWPERLRCENFPVHGAGEICVGQNTSDGSGGPGGGPTAYPTAPY
LPDLPFTALPPGASDGRGRPAFPFSCPRQLKVPPYLGYRFLGERDCGAPCEPGRANGLMYF
KEEERRFARLWVGVWSVLCCASTLFTVLTYLVDMRRFSYPERPIIFLSGCYFMVAVAHVA
GFLLEDRAVCVERFSDDGYRTVAQGTKKEGCTILFMVLYFFGMASSIWWVILSLTWFLAA
GMKWGHEAIEANSQYFHLAAWAVPAVKTITILAMGQVDGDLLSGVCYVGLSSVDA
LRGFVLAPLFVYLFIGTSFLLAGFVSLFRIRTIMKHDGTKTEKLEKLMVRIGVFSVLYTVPAT
IVLACYFYEQAFREHWERTWLLQTCKSYAVPCPPGHFPPMSPDFTVFMIKYLMTMIVGITT
GFWIWSGKTLQSWRRFYHRLSHSSKGETAV

Figure71

ACAGCATGGAGTGGGGTTACCTGTTGGAAGTGACCTCGCTGCTGGCCGCCTTGGCGCT
GCTGCAGCGCTCTAGCGGCGCTGCGGCCGCCTCGGCCAAGGAGCTGGCATGCCAAGAG
ATCACCGTGCCGCTGTGTAAGGGCATCGGCTACAACTACACCTACATGCCCAATCAGTT
CAACCACGACACGCAAGACGAGGCGGGCCTGGAGGTGCACCAGTTCTGGCCGCTGGTG
GAGATCCAGTGCTCGCCCGATCTCAAGTTCTTCCTGTGCAGCATGTACACGCCCATCTG
CCTAGAGGACTACAAGAAGCCGCTGCCGCCCTGCCGCTCGGTGTGCGAGCGCGCCAAG
GCCGGCTGCGCGCCGCTCATGCGCCAGTACGGCTTCGCCTGGCCCGACCGCATGCGCT
GCGACCGGCTGCCCGAGCAAGGCAACCCTGACACGCTGTGCATGGACTACAACCGCAC
CGACCTAACCACCGCCGCGCCCAGCCCGCCGCGCCGCCTGCCGCCGCCGCCGCCCGGC
GAGCAGCCGCCTTCGGGCAGCGGCCACGGCCGCCCGCCGGGGGCCAGGCCCCCGCACC
GCGGAGGCGGCAGGGGCGGTGGCGGCGGGGACGCGGCGGCGCCCCCAGCTCGCGGCG
GCGGCGGTGGCGGGAAGGCGCGGCCCCCTGGCGGCGGCGCGGCTCCCTGCGAGCCCG
GGTGCCAGTGCCGCGCGCCTATGGTGAGCGTGTCCAGCGAGCGCCACCCGCTCTACAA
CCGCGTCAAGACAGGCCAGATCGCTAACTGCGCGCTGCCCTGCCACAACCCCTTTTTCA
GCCAGGACGAGCGCGCCTTCACCGTCTTCTGGATCGGCCTGTGGTCGGTGCTCTGCTTC
GTGTCCACCTTCGCCACCGTCTCCACCTTCCTTATCGACATGGAGCGCTTCAAGTACCC
GGAGCGGCCCATTATCTTCCTCTCGGCCTGCTACCTCTTCGTGTCGGTGGGCTACCTAG
TGCGCCTGGTGGCGGGCCACGAGAAGGTGGCGTGCAGCGGTGGCGCGCCGGGCGCGG
GGGGCGCTGGGGGCGCGGGCGGCGCGGCGGCGGGCGCGGGCGCGGCGGGCGCGGGCG
CGGGCGGCCCGGGCGGGCGCGGCGAGTACGAGGAGCTGGGCGCGGTGGAGCAGCACG
TGCGCTACGAGACCACCGGCCCCGCGCTGTGCACCGTGGTCTTCTTGCTGGTCTACTTC
TTCGGCATGGCCAGCTCCATCTGGTGGGTGATCTTGTCGCTCACATGGTTCCTGGCGGC
CGGTATGAAGTGGGGCAACGAAGCCATCGCCGGCTACTCGCAGTACTTCCACCTGGCC
GCGTGGCTTGTGCCCAGCGTCAAGTCCATCGCGGTGCTGGCGCTCAGCTCGGTGGACG
GCGACCCGGTGGCGGGCATCTGCTACGTGGGCAACCAGAGCCTGGACAACCTGCGCGG
CTTCGTGCTGGCGCCGCTGGTCATCTACCTCTTCATCGGCACCATGTTCCTGCTGGCCG
GCTTCGTGTCCCTGTTCCGCATCCGCTCGGTCATCAAGCAACAGGACGGCCCCACCAAG
ACGCACAAGCTGGAGAAGCTGATGATCCGCCTGGGCCTGTTCACCGTGCTCTACACCG
TGCCCGCCGCGGTGGTGGTCGCCTGCCTCTTCTACGAGCAGCACAACCGCCCCGCGCTG
GGAGGCCACGCACAACTGCCCGTGCCTGCGGGACCTGCAGCCCGACCAGGCACGCAG
GCCCGACTACGCCGTCTTCATGCTCAAGTACTTCATGTGCCTAGTGGTGGGCATCACCT
CGGGCGTGTGGGTCTGGTCCGGCAAGACGCTGGAGTCCTGGCGCTCCCTGTGCACCCG
CTGCTGCTGGGCCAGCAAGGGCGCCGCGGTGGGCGGGGGCGCGGGCGCCACGGCCGC

GGCCGGGCGGCGGCGGGGGCTCCCTCTACAGCGACGTCAGCACTGGCCTGACGTGGCG
GTCGGGCACGGCGAGCTCCGTGTCTTATCCAAAGCAGATGCCATTGTCCCAGGTCTGA
GCGGAGGGGAGGGGGCGCCCAGGAGGGGTGGGAGGGGGGCGAGGAGACCCAAGTG
CAGCGAAGGGACACTTGATGGGCTGAGGTTCCCACCCCTTCACAGTGTTGATTGCTATT
AGCATGATAATGAACTCTTAATGGTATCCATTAGCTGGGACTTAAATGACTCACTTAGA
ACAAAGTACCTGGCATTGAAGCCTCCCAGACCCAGCCCCTTTTCCTCCATTGATGTGCG
GGGAGCTCCTCCCGCCACGCGTTAATTTCTGTTGGCTGAGGAGGGTGGACTCTGCGGCG
TTTCCAGAACCCGAGATTTGGAGCCCTCCCTGGCTGCACTTGGCTGGGTTTGCAGTCAG
ATACACAGATTTCACCTGGGAGAACCTCTTTTTCTCCCTCGACTCTTCCTACGTAAACTC
CCACCCCTGACTTACCCTGGAGGAGGGGTGACCGCCACCTGATGGGATTGCACGGTTT
GGGTATTCTTAATGACCAGGCAAATGCCTTAAGTAAACAAACAAGAAATGTCTTAATT
ATACACCCCACGTAAATACGGGTTTCTTACATTAGAGGATGTATTTATATAATTATTTG
TTAAATTGTAAAAAAAAAAAAGTGTAAAATATGTATATATCCAAAGATATAGTGTGTAC
ATTTTTTTGTAAAAAGTTTAGAGGCTTACCCCTGTAAGAACAGATATAAGTATTCTATT
TTGTCAATAAAATGACTTTTGATAAATGATTTAACCATTGCCCTCTCCCCCGCCTCTTCT
GAGCTGTCACCTTTAAAGTGCTTGCTAAGGACGCATGGGGAAAATGGACATTTTCTGG
CTTGTCATTCTGTACACTGACCTTAGGCATGGAGAAAATTACTTGTTAAACTCTAGTTC
TTAAGTTGTTAGCCAAGTAAATATCATTGTTGAACTGAAATCAAAATTGAGTTTTTGCA
CCTTCCCCAAAGACGGTGTTTTTCATGGGAGCTCTTTTCTGATCCATGGATAACAACTC
TCACTTTAGTGGATGTAAATGGAACTTCTGCAAGGCAGTAATTCCCCTTAGGCCTTGTT
ATTTATCCTGCATGGTATCACTAAAGGTTTCAAAACCCTGAAAAAAAA

Figure 72

MEWGYLLEVTSLLAALALLQRSSGAAAASAKELACQEITVPLCKGIGYNYTYMPNQFNHD
TQDEAGLEVHQFWPLVEIQCSPDLKFFLCSMYTPICLEDYKKPLPPCRSVCERAKAGCAPL
MRQYGFAWPDRMRCDRLPEQGNPDTLCMDYNRTDLTTAAPSPPRRLPPPPPGEQPPSGSG
HGRPPGARPPHRGGGRGGGGGDAAAPPARGGGGGGKARPPGGGAAPCEPGCQCRAPMVS
VSSERHPLYNRVKTGQIANCALPCHNPFFSQDERAFTVFWIGLWSVLCFVSTFATVSTFLID
MERFKYPERPIIFLSACYLFVSVGYLVRLVAGHEKVACSGGAPGAGGAGGAGGAAAGAG
AAGAGAGGPGGRGEYEELGAVEQHVRYETTGPALCTVVFLLVYFFGMASSIWWVILSLT
WFLAAGMKWGNEAIAGYSQYFHLAAWLVPSVKSIAVLALSSVDGDPVAGICYVGNQSLD
NLRGFVLAPLVIYLFIGTMFLLAGFVSLFRIRSVIKQQDGPTKTHKLEKLMIRLGLFTVLYTV
PAAVVVACLFYEQHNRPRWEATHNCPCLRDLQPDQARRPDYAVFMLKYFMCLVVGITSG
VWVWSGKTLESWRSLCTRCCWASKGAAVGGGAGATAAGGGGGPGGGGGGGPGGGGGP
GGGGGSLYSDVSTGLTWRSGTASSVSYPKQMPLSQV

Figure 73

CCGCCTTCGGCCCGGGCCTCCCGGGATGGCCGTGGCGCCTCTGCGGGGGGCGCTGCTG
CTGTGGCAGCTGCTGGCGGCGGGCGGCGCGGCACTGGAGATCGGCCGCTTCGACCCGG
AGCGCGGGCGCGGGGCTGCGCCGTGCCAGGCGGTGGAGATCCCCATGTGCCGCGGCAT
CGGCTACAACCTGACCCGCATGCCCAACCTGCTGGGCCACACGTCGCAGGGCGAGGCG
GCTGCCGAGCTAGCGGAGTTCGCGCCGCTGGTGCAGTACGGCTGCCACAGCCACCTGC
GCTTCTTCCTGTGCTCGCTCTACGCGCCCATGTGCACCGACCAGGTCTCGACGCCCATT
CCCGCCTGCCGGCCCATGTGCGAGCAGGCGCGCCTGCGCTGCGCGCCCATCATGGAGC
AGTTCAACTTCGGCTGGCCGGACTCGCTCGACTGCGCCCGGCTGCCCACGCGCAACGA
CCCGCACGCGCTGTGCATGGAGGCGCCCGAGAACGCCACGGCCGGCCCCGCGGAGCCC

TGGGCCCGGGCGCGGGCGGCAGTGGCACCTGCGAGAACCCCGAGAAGTTCCAGTACGT
GGAGAAGAGCCGCTCGTGCGCACCGCGCTGCGGGCCCGGCGTCGAGGTGTTCTGGTCC
CGGCGCGACAAGGACTTCGCGCTGGTCTGGATGGCCGTGTGGTCGGCGCTGTGCTTCTT
CTCCACCGCCTTCACTGTGCTCACCTTCTTGCTGGAGCCCCACCGCTTCCAGTACCCCG
AGCGCCCCATCATCTTCCTCTCCATGTGCTACAACGTCTACTCGCTGGCCTTCCTGATCC
GTGCGGTGGCCGGAGCGCAGAGCGTGGCCTGTGACCAGGAGGCGGGCGCGCTCTACGT
GATCCAGGAGGGCCTGGAGAACACGGGCTGCACGCTGGTCTTCCTACTGCTCTACTAC
TTCGGCATGGCCAGCTCGCTCTGGTGGGTGGTCCTGACGCTCACCTGGTTCCTGGCTGC
CGGGAAGAAATGGGGCCACGAGGCCATCGAGGCCCACGGCAGCTATTTCCACATGGCT
GCCTGGGGCCTGCCCGCGCTCAAGACCATCGTCATCCTGACCCTGCGCAAGGTGGCGG
GTGATGAGCTGACTGGGCTTTGCTACGTGGCCAGCACGGATGCAGCAGCGCTCACGGG
CTTCGTGCTGGTGCCCCTCTCTGGCTACCTGGTGCTGGGCAGTAGTTTCCTCCTGACCG
GCTTCGTGGCCCTCTTCCACATCCGCAAGATCATGAAGACGGGCGGCACCAACACAGA
GAAGCTGGAGAAGCTCATGGTCAAGATCGGGGTCTTCTCCATCCTCTACACGGTGCCC
GCCACCTGCGTCATCGTTTGCTATGTCTACGAACGCCTCAACATGGACTTCTGGCGCCT
TCGGGCCACAGAGCAGCCATGCGCAGCGGCCGCGGGGCCCGGAGGCCGGAGGGACTG
CTCGCTGCCAGGGGGCTCGGTGCCCACCGTGGCGGTCTTCATGCTCAAAATTTTCATGT
CACTGGTGGTGGGGATCACCAGCGGCGTCTGGGTGTGGAGCTCCAAGACTTTCCAGAC
CTGGCAGAGCCTGTGCTACCGCAAGATAGCAGCTGGCCGGGCCCGGGCCAAGGCCTGC
CGCGCCCCCGGGAGCTACGGACGTGGCACGCACTGCCACTATAAGGCTCCCACCGTGG
TCTTGCACATGACTAAGACGGACCCCTCTTTGGAGAACCCCACACACCTCTAGCCACAC
AGGCCTGGCGCGGGGTGGCTGCTGCCCCCTCCTTGCCCTCCACGCCCTGCCCCCTGCAT
CCCCTAGAGACAGCTGACTAGCAGCTGCCCAGCTGTCAAGGTCAGGCAAGTGAGCACC
GGGGACTGAGGATCAGGGCGGGACCCCGTGAGGCTCATTAGGGGAGATGGGGGTCTC
CCCTAATGCGGGGGCTGGACCAGGCTGAGTCCCCACAGGGTCCTAGTGGAGGATGTGG
AGGGGCGGGGCAGAGGGGTCCAGCCGGAGTTTATTTAATGATGTAATTTATTGTTGCG
TTCCTCTGGAAGCTGTGACTGGAATAAACCCCCGCGTGGCACTGCTGATCCTCTCTGGC
TGGGAAGGGGGAAGGTAGGAGGTGAGGC

Figure 74

MAVAPLRGALLLWQLLAAGGAALEIGRFDPERGRGAAPCQAVEIPMCRGIGYNLTRMPNL
LGHTSQGEAAAELAEFAPLVQYGCHSHLRFFLCSLYAPMCTDQVSTPIPACRPMCEQARLR
CAPIMEQFNFGWPDSLDCARLPTRNDPHALCMEAPENATAGPAEPHKGLGMLPVAPRPAR
PPGDLGPGAGGSGTCENPEKFQYVEKSRSCAPRCGPGVEVFWSRRDKDFALVWMAVWSA
LCFFSTAFTVLTFLLEPHRFQYPERPIIFLSMCYNVYSLAFLIRAVAGAQSVACDQEAGALY
VIQEGLENTGCTLVFLLLYYFGMASSLWWVVLTLTWFLAAGKKWGHEAIEAHGSYFHMA
AWGLPALKTIVILTLRKVAGDELTGLCYVASTDAAALTGFVLVPLSGYLVLGSSFLLTG
FVALFHIRKIMKTGGTNTEKLEKLMVKIGVFSILYTVPATCVIVCYVYERLNMDFWRLRAT
EQPCAAAAGPGGRRDCSLPGGSVPTVAVFMLKIFMSLVVGITSGVWVWSSKTFQTWQSLC
YRKIAAGRARAKACRAPGSYGRGTHCHYKAPTVVLHMTKTDPSLENPTHL

Figure 75

ACACGTCCAACGCCAGCATGCAGCGCCCGGGCCCCCGCCTGTGGCTGGTCCTGCAGGT
GATGGGCTCGTGCGCCGCCATCAGCTCCATGGACATGGAGCGCCCGGGCGACGGCAAA
TGCCAGCCCATCGAGATCCCGATGTGCAAGGACATCGGCTACAACATGACTCGTATGC
CCAACCTGATGGGCCACGAGAACCAGCGCGAGGCAGCCATCCAGTTGCACGAGTTCGC
GCCGCTGGTGGAGTACGGCTGCCACGGCCACCTCCGCTTCTTCCTGTGCTCGCTGTACG
CGCCGATGTGCACCGAGCAGGTCTCTACCCCCATCCCCGCCTGCCGGGTCATGTGCGA
GGACGGCGGCCTGAACTGCTCCCCGATTATGGAGCAGTTCAACTTCAAGTGGCCCGAC

TCCCTGGACTGCCGGAAACTCCCCAACAAGAACGACCCCAACTACCTGTGCATGGAGG
CGCCCAACAACGGCTCGGACGAGCCCACCCGGGGCTCGGGCCTGTTCCCGCCGCTGTT
CCGGCCGCAGCGGCCCCACAGCGCGCAGGAGCACCCGCTGAAGGACGGGGGCCCCGG
GCGCGGCGGCTGCGACAACCCGGGCAAGTTCCACCACGTGGAGAAGAGCGCGTCGTG
CGCGCCGCTCTGCACGCCCGGCGTGGACGTGTACTGGAGCCGCGAGGACAAGCGCTTC
GCAGTGGTCTGGCTGGCCATCTGGGCGGTGCTGTGCTTCTTCTCCAGCGCCTTCACCGT
GCTCACCTTCCTCATCGACCCGGCCCGCTTCCGCTACCCCGAGCGCCCCATCATCTTCC
TCTCCATGTGCTACTGCGTCTACTCCGTGGGCTACCTCATCCGCCTCTTCGCCGGCGCC
GAGAGCATCGCCTGCGACCGGGACAGCGGCCAGCTCTATGTCATCCAGGAGGGACTGG
AGAGCACCGGCTGCACGCTGGTCTTCCTGGTCCTCTACTACTTCGGCATGGCCAGCTCG
CTGTGGTGGGTGGTCCTCACGCTCACCTGGTTCCTGGCCGCCGGCAAGAAGTGGGGCC
ACGAGGCCATCGAAGCCAACAGCAGCTACTTCCACCTGGCAGCCTGGGCCATCCCGGC
GGTGAAGACCATCCTGATCCTGGTCATGCGCAGGGTGGCGGGGGACGAGCTCACCGGG
GTCTGCTACGTGGGCAGCATGGACGTCAACGCGCTCACCGGCTTCGTGCTCATTCCCCT
GGCCTGCTACCTGGTCATCGGCACGTCCTTCATCCTCTCGGGCTTCGTGGCCCTGTTCC
ACATCCGGAGGGTGATGAAGACGGGCGGCGAGAACACGGACAAGCTGGAGAAGCTCA
TGGTGCGTATCGGGCTCTTCTCTGTGCTGTACACCGTGCCGGCCACCTGTGTGATCGCC
TGCTACTTTTACGAACGCCTCAACATGGATTACTGGAAGATCCTGGCGGCGCAGCACA
AGTGCAAAATGAACAACCAGACTAAAACGCTGGACTGCCTGATGGCCGCCTCCATCCC
CGCCGTGGAGATCTTCATGGTGAAGATCTTTATGCTGCTGGTGGTGGGGATCACCAGCG
GGATGTGGATTTGGACCTCCAAGACTCTGCAGTCCTGGCAGCAGGTGTGCAGCCGTAG
GTTAAAGAAGAAGAGCCGGAGAAAACCGGCCAGCGTGATCACCAGCGGTGGGATTTA
CAAAAAAGCCCAGCATCCCCAGAAAACTCACCACGGGAAATATGAGATCCCTGCCCAG
TCGCCCACCTGCGTGTGAACAGGGCTGGAGGGAAGGGCACAGGGGCGCCCGGAGCTA
AGATGTGGTGCTTTTCTTGGTTGTGTTTTTCTTTCTTCTTCTTCTTTTTTTTTTTTTATAA
AAGCAAAAGAGAAATACATAAAAAAGTGTTTACCCTGAAATTCAGGATGCTGTGATAC
ACTGAAAGGAAAAATGTACTTAAAGGGTTTTGTTTTGTTTTGGTTTTCCAGCGAAGGGA
AGCTCCTCCAGTGAAGTAGCCTCTTGTGTAACTAATTTGTGGTAAAGTAGTTGATTCAG
CCCTCAGAAGAAAACTTTTGTTTAGAGCCCTCCGTAAATATACATCTGTGTATTTGAGT
TGGCTTTGCTACCCATTTACAAATAAGAGGACAGATAACTGCTTTGCAAATTCAAGAGC
CTCCCCTGGGTTAACAAATGAGCCATCCCCAGGGCCCACCCCCAGGAAGGCCACAGTG
CTGGGCGGCATCCCTGCAGAGGAAAGACAGGACCCGGGGCCCGCCTCACACCCCAGTG
GATTTGGAGTTGCTTAAAATAGACTCTGGCCTTCACCAATAGTCTCTCTGCAAGACAGA
AACCTCCATCAAACCTCACATTTGTGAACTCAAACGATGTGCAATACATTTTTTTCTCTT
TCCTTGAAAATAAAAAGAGAAACAAGTATTTTGCTATATATAAAGACAACAAAAGAAA
TCTCCTAACAAAAGAACTAAGAGGCCCAGCCCTCAGAAACCCTTCAGTGCTACATTTT
GTGGCTTTTTAATGGAAACCAAGCCAATGTTATAGACGTTTGGACTGATTTGTGGAAAG
GAGGGGGGAAGAGGGAGAAGGATCATTCAAAAGTTACCCAAAGGGCTTATTGACTCTT
TCTATTGTTAAACAAATGATTTCCACAAACAGATCAGGAAGCACTAGGTTGGCAGAGA
CACTTTGTCTAGTGTATTCTCTTCACAGTGCCAGGAAAGAGTGGTTTCTGCGTGTGTAT
ATTTGTAATATATGATATTTTTCATGCTCCACTATTTTATTAAAAATAAAATATGTTCTT
TAAAAAAA

Figure 76

MQRPGPRLWLVLQVMGSCAAISSMDMERPGDGKCQPIEIPMCKDIGYNMTRMPNLMGHE
NQREAAIQLHEFAPLVEYGCHGHLRFFLCSLYAPMCTEQVSTPIPACRVMCEQARLKCSPI
MEQFNFKWPDSLDCRKLPNKNDPNYLCMEAPNNGSDEPTRGSGLFPPLFRPQRPHSAQEH
PLKDGGPGRGGCDNPGKFHHVEKSASCAPLCTPGVDVYWSREDKRFAVVWLAIWAVLCF
FSSAFTVLTFLIDPARFRYPERPIIFLSMCYCVYSVGYLIRLFAGAESIACDRDSGQLYVIQEG
LESTGCTLVFLVLYYFGMASSLWWVVLTLTWFLAAGKKWGHEAIEANSSYFHLAAWAIP
AVKTILLVMRRVAGDELTGVCYVGSMDVNALTGFVLIPLACYLVIGTSFILSGFVAL

FHIRRVMKTGGENTDKLEKLMVRIGLFSVLYTVPATCVIACYFYERLNMDYWKILAAQHK
CKMNNQTKTLDCLMAASIPAVEIFMVKIFMLLVVGITSGMWIWTSKTLQSWQQVCSRRLK
KKSRRKPASVITSGGIYKKAQHPQKTHHGKYEIPAQSPTCV

Figure 77

CCTGCAGCCTCCGGAGTCAGTGCCGCGCGCCCGCCGCCCCGCGCCTTCCTGCTCGCCGC
ACCTCCGGGAGCCGGGGCGCACCCAGCCCGCAGCGCCGCCTCCCCGCCCGCGCCGCCT
CCGACCGCAGGCCGAGGGCCGCCACTGGCCGGGGGACCGGGCAGCAGCTTGCGGCC
GCGGAGCCGGGCAACGCTGGGGACTGCGCCTTTTGTCCCCGGAGGTCCCTGGAAGTTT
GCGGCAGGACGCGCGCGGGGAGGCGGCGGAGGCAGCCCCGACGTCGCGGAGAACAGG
GCGCAGAGCCGGCATGGGCATCGGGCGCAGCGAGGGGGGCCGCCGCGGGGCCCTGGG
CGTGCTGCTGGCGCTGGGCGCGGCGCTTCTGGCCGTGGGCTCGGCCAGCGAGTACGAC
TACGTGAGCTTCCAGTCGGACATCGGCCCGTACCAGAGCGGGCGCTTCTACACCAAGC
CACCTCAGTGCGTGGACATCCCCGCGGACCTGCGGCTGTGCCACAACGTGGGCTACAA
GAAGATGGTGCTGCCCAACCTGCTGGAGCACGAGACCATGGCGGAGGTGAAGCAGCA
GGCCAGCAGCTGGGTGCCCCTGCTCAACAAGAACTGCCACGCCGGGACCCAGGTCTTC
CTCTGCTCGCTCTTCGCGCCCGTCTGCCTGGACCGGCCCATCTACCCGTGTCGCTGGCT
CTGCGAGGCCGTGCGCGACTCGTGCGAGCCGGTCATGCAGTTCTTCGGCTTCTACTGGC
CCGAGATGCTTAAGTGTGACAAGTTCCCGGAGGGGGACGTCTGCATCGCCATGACGCC
GCCCAATGCCACCGAAGCCTCCAAGCCCCAAGGCACAACGGTGTGTCCTCCCTGTGAC
AACGAGTTGAAATCTGAGGCCATCATTGAACATCTCTGTGCCAGCGAGTTTGCACTGA
GGATGAAAATAAAAGAAGTGAAAAAAGAAAATGGCGACAAGAAGATTGTCCCCAAGA
AGAAGAAGCCCCTGAAGTTGGGGCCCATCAAGAAGAAGGACCTGAAGAAGCTTGTGC
TGTACCTGAAGAATGGGGCTGACTGTCCCTGCCACCAGCTGGACAACCTCAGCCACCA
CTTCCTCATCATGGGCCGCAAGGTGAAGAGCCAGTACTTGCTGACGGCCATCCACAAG
TGGGACAAGAAAAACAAGGAGTTCAAAAACTTCATGAAGAAAATGAAAAACCATGAG
TGCCCCACCTTTCAGTCCGTGTTTAAGTGATTCTCCCGGGGGCAGGGTGGGGAGGGAG
CCTCGGGTGGGGTGGGAGCGGGGGGGACAGTGCCCGGGAACCCGTGGTCACACACAC
GCACTGCCCTGTCAGTAGTGGACATTGTAATCCAGTCGGCTTGTTCTTGCAGCATTCCC
GCTCCCTTTCCCTCCATAGCCACGCTCCAAACCCCAGGGTAGCCATGGCCGGGTAAAG
CAAGGGCCATTTAGATTAGGAAGGTTTTTAAGATCCGCAATGTGGAGCAGCAGCCACT
GCACAGGAGGAGGTGACAAACCATTTCCAACAGCAACACAGCCACTAAAACACAAAA
AGGGGGATTGGGCGGAAAGTGAGAGCCAGCAGCAAAAACTACATTTTGCAACTTGTTG
GTGTGGATCTATTGGCTGATCTATGCCTTTCAACTAGAAAATTCTAATGATTGGCAAGT
CACGTTGTTTTCAGGTCCAGAGTAGTTTCTTTCTGTCTGCTTTAAATGGAAACAGACTC
ATACCACACTTACAATTAAGGTCAAGCCCAGAAAGTGATAAGTGCAGGGAGGAAAAG
TGCAAGTCCATTATCTAATAGTGACAGCAAAGGGACCAGGGGAGAGGCATTGCCTTCT
CTGCCCACAGTCTTTCCGTGTGATTGTCTTTGAATCTGAATCAGCCAGTCTCAGATGCC
CCAAAGTTTCGGTTCCTATGAGCCCGGGGCATGATCTGATCCCCAAGACATGTGGAGG
GGCAGCCTGTGCCTGCCTTTGTGTCAGAAAAAGGAAACCACAGTGAGCCTGAGAGAGA
CGGCGATTTTCGGGCTGAGAAGGCAGTAGTTTTCAAAACACATAGTTA

Figure 78

MGIGRSEGGRRGAALGVLLALGAALLAVGSASEYDYVSFQSDIGPYQSGRFYTKPPQCVDI
PADLRLCHNVGYKKMVLPNLLEHETMAEVKQQASSWVPLLNKNCHAGTQVFLCSLFAPV
CLDRPIYPCRWLCEAVRDSCEPVMQFFGFYWPEMLKCDKFPEGDVCIAMTPPNATEASKP
QGTTVCPPCDNELKSEAIIEHLCASEFGLSLKMIVGSSHNSCCTLGPSHPNSSKRQEQELGTP
EPPLCYCLLLHEIQGNLPPPCAQARSRMRLKTEATPLALGRSAPGLFADCPERPLPVCSFPH

HTEEVGKLRIHSFLLQVKGFSMKGLCAPSTLRYLYYLKTSMQHVHQEYQAHSAQVWANM
PPAERCKDEEDKAMFSK

Figure 79

GAATTCGTTCAGCCTGGTTAAGTCCAAGCTGGCTCATTCTGCTCCCCCGGGTCGGAGCC
CCCCGGAGCTGCGCGCGGGCTTGCAGCGCCTCGCCCGCGCTGTCCTCCCGGTGTCCCGC
TTCTCCGCGCCCCAGCCGCCGGCTGCCAGCTTTTCGGGGCCCCGAGTCGCACCCAGCGA
AGAGAGCGGGCCCGGGACAAGCTCGAACTCCGGCCGCCTCGCCCTTAACCAGCTCCGT
CCCTCTACCCCCTAGGGGTCGCGCCCACGATGCTGCAGGGCCCTGGCTCGCTGCTGCTG
CTCTTCCTCGCCTCGCACTGCTGCCTGGGCTCGGCGCGCGGGCTCTTCCTCTTTGGCCA
GCCCGACTTCTCCTACAAGCGCAGCAATTGCAAGCCCATCCCGGCCAACCTGCAGCTG
TGCCACGGCATCGAATACCAGAACATGCGGCTGCCCAACCTGCTGGGCCACGAGACCA
TGAAGGAGGTGCTGGAGCAGGCCGGCGCTTGGATCCCGCTGGTCATGAAGCAGTGCCA
CCCGGACACCAAGAAGTTCCTGTGCTCGCTCTTCGCCCCCGTCTGCCTCGATGACCTAG
ACGAGACCATCCAGCCATGCCACTCTCGNTGCGTGCAGGTGAAGGATCGCTGCGCCCC
GGTCATGTCCGCCTTCCCCTGGCCCGACATGCTTGAGTGCGACCGTTTCCCCCAGGACA
ACGACCTTTGCATCCCCCTCGCTAGCAGCGACCACCTCCTGCCAGCCACCGAGGAAGC
TCCAAAGGTATGTGAAGCCTGCAAAAATAAAAATGATGATGACAACGACATAATGGA
AACGCTTTGTAAAAATGATTTTGCACTGAAAATAAAAGTGAAGGAGATAACCTACATC
AACCGT

Figure 80

MLQGPGSLLLLFLASHCCLGSARGLFLFGQPDFSYKRSNCKPIPANLQLCHGIEYQNMRLP
NLLGHETMKEVLEQAGAWIPLVMKQCHPDTKKFLCSLFAPVCLDDLDETIQPCHSRCVQV
KDRCAPVMSAFPWPDMLECDRFPQDNDLCIPLASSDHLLPATEEAPKVCEACKNKNDDDN
DIMETLCKNDFALKIKVKEITYINR

Figure 81

CCGGGTCGGAGCCCCCCGGAGCTGCGCGCGGGCTTGCAGCGCCTCGCCCGCGCTGTCC
TCCCGGTGTCCCGCTTCTCCGCGCCCCAGCCGCCGGCTGCCAGCTTTTCGGGGCCCCGA
GTCGCACCCAGCGAAGAGAGCGGGCCCGGGACAAGCTCGAACTCCGGCCGCCTCGCCC
TTCCCCGGCTCCGCTCCCTCTGCCCCCTCGGGGTCGCGCGCCCACGATGCTGCAGGGCC
CTGGCTCGCTGCTGCTGCTCTTCCTCGCCTCGCACTGCTGCCTGGGCTCGGCGCGCGGG
CTCTTCCTCTTTGGCCAGCCCGACTTCTCCTACAAGCGCAGCAATTGCAAGCCCATC
CCTGCCAACCTGCAGCTGTGCCACGGCATCGAATACCAGAACATGCGGCTGCCCAACC
TGCTGGGCCACGAGACCATGAAGGAGGTGCTGGAGCAGGCCGGCGCTTGGATCCCGCT
GGTCATGAAGCAGTGCCACCCGGACACCAAGAAGTTCCTGTGCTCGCTCTTCGCCCCC
GTCTGCCTCGATGACCTAGACGAGACCATCCAGCCATGCCACTCGCTCTGCGTGCAGGT
GAAGGACCGCTGCGCCCCGGTCATGTCCGCCTTCGGCTTCCCCTGGCCCGACATGCTTG
AGTGCGACCGTTTCCCCCAGGACAACGACCTTTGCATCCCCCTCGCTAGCAGCGACCA
CCTCCTGCCAGCCACCGAGGAAGCTCCAAAGGTATGTGAAGCCTGCAAAAATAAAAAT
GATGATGACAACGACATAATGGAAACGCTTTGTAAAAATGATTTTGCACTGAAAATAA

GCAAGACCATTTACAAGCTGAACGGTGTGTCCGAAAGGACCTGAAGAAATCGGTGCT
GTGGCTCAAAGACAGCTTGCAGTGCACCTGTGAGGAGATGAACGACATCAACGCGCCC
TATCTGGTCATGGGACAGAAACAGGGTGGGGAGCTGGTGATCACCTCGGTGAAGCGGT
GGCAGAAGGGGCAGAGAGAGTTCAAGCGCATCTCCCGCAGCATCCGCAAGCTGCAGT
GCTAGTCCCGGCATCCTGATGGCTCCGACAGGCCTGCTCCAGAGCACGGCTGACCATTT
CTGCTCCGGGATCTCAGCTCCCGTTCCCCAAGCACACTCCTAGCTGCTCCAGTCTCAGC
CTGGGCAGCTTCCCCCTGCCTTTTGCACGTTTGCATCCCCAGCATTTCCTGAGTTATAAG
GCCACAGGAGTGGATAGCTGTTTTCACCTAAAGGAAAAGCCCACCCGA
ATCTTGTAGAAATATTCAAACTAATAAAATCATGAATATTTTTATGAAGTTT

Figure 82

MLQGPGSLLLLFLASHCCLGSARGLFLFGQPDFSYKRSNCKPIPANLQLCHGIEYQNMRLP
NLLGHETMKEVLEQAGAWIPLVMKQCHPDTKKFLCSLFAPVCLDDLDETIQPCHSLCVQV
KDRCAPVMSAFGFPWPDMLECDRFPQDNDLCIPLASSDHLLPATEEAPKVCEACKNKNDD
DNDIMETLCKNDFALKIKVKEITYINRDTKIILETKSKTIYKLNGVSERDLKKSVLWLKDSL
QCTCEEMNDINAPYLVMGQKQGGELVITSVKRWQKGQREFKRISRSIRKLQC

Figure 83

ACGGGGCCTGGGCGGSAGGGGCGGTGGCTGGAGCTCGGTAAAGCTCGTGGGACCCCAT
TGGGGGAATTTGATCCAAGGAAGCGGTGATTGCCGGGGGAGGAGAAGCTCCCAGATCC
TTGTGTCCACTTGCAGCGGGGGAGGCGGAGACGCGGAGCGGGCCTTTTGGCGTCCACT
GCGCGGCTGCACCCTGCCCCATCCTGCCGGGATCATGGTCTGCGGCAGCCCGGGAGGG
ATGCTGCTGCTGCGGGCCGGGCTGCTTGCCCTGGCTGCTCTCTGCCTGCTCCGGGTGCC
CGGGGCTCGGGCTGCAGCCTGTGAGCCCGTCCGCATCCCCCTGTGCAAGTCCCTGCCCT
GGAACATGACTAAGATGCCCAACCACCTGCACCACAGCACTCAGGCCAACGCCATCCT
GGCCATCGAGCAGTTCGAAGGTCTGCTGGGCACCCACTGCAGCCCCGATCTGCTCTTCT
TCCTCTGTGCCATGTACGCGCCCATCTGCACCATTGACTTCCAGCACGAGCCCATCAAC
CCCTGTAAGTCTGTGTGCGAGCGGGCCCGGCAGGGCTGTGAGCCCATACTCATCAAGT
ACCGCCACTCGTGGCCGGAGAACCTGGCCTGCGAGGAGCTGCCAGTGTACGACAGGGG
CGTGTGCATCTCTCCCGAGGCCATCGTTACTGCGGACGGAGCTGATTTTCCTATGGATT
CTAGTAACGGAAACTGTAGAGGGGCAAGCAGTGAACGCTGTAAATGTAAGCCTATTAG
AGCTACACAGAAGACCTATTTCCGGAACAATTACAACTATGTCATTCGGGCTAAAGTT
AAAGAGATAAAGACTAAGTGCCATGATGTGACTGCAGTAGTGGAGGTGAAGGAGATT
CTAAAGTCCTCTCTGGTAAACATTCCACGGGACACTGTCAACCTCTATACCAGCTCTGG
CTGCCTCTGCCCTCCACTTAATGTTAATGAGGAATATATCATCATGGGCTATGAAGATG
AGGAACGTTCCAGATTACTCTTGGTGGAAGGCTCTATAGCTGAGAAGTGGAAGGATCG
ACTCGGTAAAAAAGTTAAGCGCTGGGATATGAAGCTTCGTCATCTTGGACTCAGTAAA
AGTGATTCTAGCAATAGTGATTCCACTCAGAGTCAGAAGTCTGGCAGGAACTCGAACC
CCCGGCAAGCACGCAACTAAATCCCGAAATACAAAAAGTAACACAGTGGACTTCCTAT
TAAGACTTACTTGCATTGCTGGACTAGCAAAGGAAAATTGCACTATTGCACATCATATT
CTATTGTTTACTATAAAAATCATGTGATAACTGATTATTACTTCTGTTTCTCTTTTGGTTT
CTGCTTCTCTCTTCTCTCAACCCCTTTGTAATGGTTTGGGGGCAGACTCTTAAGTATATT
GTGAGTTTTCTATTTCACTAATCATGAGAAAAACTGTTCTTTTGCAATAATAATAAATT
AAACATGCTGTTA

Figure 84

MVCGSPGGMLLLRAGLLALAALCLLRVPGARAAACEPVRIPLCKSLPWNMTKMPNHLHH
STQANAILAIEQFEGLLGTHCSPDLLFFLCAMYAPICTIDFQHEPIKPCKSVCERARQGCEPIL
IKYRHSWPENLACEELPVYDRGVCISPEAIVTADGADFPMDSSNGNCRGASSERCKCKPIR
ATQKTYFRNNYNYVIRAKVKEIKTKCHDVTAVVEVKEILKSSLVNIPRDTVNLYTSSGCLC
PPLNVNEEYIIMGYEDEERSRLLLVEGSIAEKWKDRLGKKVKRWDMKLRHLGLSKSDSSN
SDSTQSQKSGRNSNPRQARN

Figure 85

CAGCGGCCGCTGAATTCTAGGGCGGGTTCGCGCCCCGAAGGCTGAGAGCTGGCGCTGC
TCGTGCCCTGTGTGCCAGACGGCGGAGCTCCGCGGCCGGACCCCGCGGCCCCGCTTTG
CTGCCGACTGGAGTTTGGGGGAAGAAACTCTCCTGCGCCCCAGAAGATTTCTTCCTCGG
CGAAGGGACAGCGAAAGATGAGGGTGGCAGGAAGAGAAGGCGCTTTCTGTCTGCCGG
GGTCGCAGCGCGAGAGGGCAGTGCCATGTTCCTCTCCATCCTAGTGGCGCTGTGCCTGT
GGCTGCACCTGGCGCTGGGCGTGCGCGGCGCGCCCTGCGAGGCGGTGCGCATCCCTAT
GTGCCGGCACATGCCCTGGAACATCACGCGGATGCCCAACCACCTGCACCACAGCACG
CAGGAGAACGCCATCCTGGCCATCGAGCAGTACGAGGAGCTGGTGGACGTGAACTGC
AGCGCCGTGCTGCGCTTCTTCTTCTGTGCCATGTACGCGCCCATTTGCACCCTGGAGTT
CCTGCACGACCCTATCAAGCCGTGCAAGTCGGTGTGCCAACGCGCGCGCGACGACTGC
GAGCCCCTCATGAAGATGTACAACCACAGCTGGCCCGAAAGCCTGGCCTGCGACGAGC
TGCCTGTCTATGACCGTGGCGTGTGCATTTCGCCTGAAGCCATCGTCACGGACCTCCCG
GAGGATGTTAAGTGGATAGACATCACACCAGACATGATGGTACAGGAAAGGCCTCTTG
ATGTTGACTGTAAACGCCTAAGCCCCGATCGGTGCAAGTGTAAAAAGGTGAAGCCAAC
TTTGGCAACGTATCTCAGCAAAAACTACAGCTATGTTATTCATGCCAAAATAAAAGCTG
TGCAGAGGAGTGGCTGCAATGAGGTCACAACGGTGGTGGATGTAAAAGAGATCTTCAA
GTCCTCATCACCCATCCCTCGAACTCAAGTCCCGCTCATTACAAATTCTTCTTGCCAGT
GTCCACACATCCTGCCCCATCAAGATGTTCTCATCATGTGTTACGAGTGGCGTTCAAGG
ATGATGCTTCTTGAAAATTGCTTAGTTGAAAAATGGAGAGATCAGCTTAGTAAAAGAT
CCATACAGTGGGAAGAGAGGCTGCAGGAACAGCGGAGAACAGTTCAGGACAAGAAGA
AAACAGCCGGGCGCACCAGTCGTAGTAATCCCCCCAAACCAAAGGGAAAGCCTCCTGC
TCCCAAACCAGCCAGTCCCAAGAAGAACATTAAAACTAGGAGTGCCCAGAAGAGAAC
AAACCCGAAAAGAGTGTGAGCTAACTAGTTTCCAAAGCGGAGACTTCCGACTTCCTTA
CAGGATGAGGCTGGGCATTGCCTGGGACAGCCTATGTAAGGCCATGTGCCCCTTGCCC
TAACAACTCACTGCAGTGCTCTTCATAGACACATCTTGCAGCATTTTTCTTAAGGCTAT
GCTTCAGTTTTTCTTTGTAAGCCATCACAAGCCATAGTGGTAGGTTTGCCCTTTGGTACA
GAAGGTGAGTTAAAGCTGGTGGAAAAGGCTTATTGCATTGCATTCAGAGTAACCTGTG
TGCATACTCTAGAAGAGTAGGGAAAATAATGCTTGTTACAATTCGACCTAATATGTGC
ATTGTAAAATAAATGCCATATTTCAAACAAAACACGTAATTTTTTTACAGTATGTTTTA
TTACCTTTTGATATCTGTTGTTGCAATGTTAGTGATGTTTTAAAATGTGATGAAAATATA
ATGTTTTTAAGAAGGAACAGTAGTGGAATGAATGTTAAAAGATCTTTATGTGTTTATGG
TCTGCAGAAGGATTTTTGTGATGAAAGGGGATTTTTTGAAAAATTAGAGAAGTAGCAT
ATGGAAAATTATAATGTGTTTTTTTACCAATGACTTCAGTTTCTGTTTTTAGCTAGAAAC
TTAAAAACAAAAATAATAATAAAGAAAAATAAATAAAAAGGAGAGGCAGACAATGTC
TGGATTCCTGTTTTTTGGTTACCTGATTTCCATGATCATGATGCTTCTTGTCAACACCCT
CTTAAGCAGCACCAGAAACAGTGAGTTTGTCTGTACCATTAGGAGTTAGGTACTAATTA
GTTGGCTAATGCTCAAGTATTTTATACCCACAAGAGAGGTATGTCACTCATCTTACTTC
CCAGGACATCCACCCTGAGAATAATTTGACAAGCTTAAAAATGGCCTTCATGTGAGTG
CCAAATTTTGTTTTTCTTCATTTAAATATTTTCTTTGCCTAAATACATGTGAGAGGAGTT
AAATATAAATGTACAGAGAGGAAAGTTGAGTTCCACCTCTGAAATGAGAATTACTTGA
CAGTTGGGATACTTTAATCAGAAAAAAAGAACTTATTTGCAGCATTTTATCAACAAATT
TGATAAATTCTGGAGAATTGCAGGCATTTATTTTAAAAAACAATTTTATTGGCCTTTTGCT

AACACAGTAAGCATGTATTTTATAAGGCATTCAATAAATGCACAACGCCCAAAGGAAA
TAAAATCCTATCTAATCCTACTCTCCACTACACAGAGGTAATCACTATTAGTATTTGG
CATATTATTCTCCAGGTGTTTGCTTATGCACTTATAAAATGATTTGAACAAATAAAACT
AGGAACCTGTATACATGTGTTTCATAACCTGCCTCCTTTGCTTGGCCCTTTATTGAGATA
AGTTTTCCTGTCAAGAAAGCAGAAACCATCTCATTTCTAACAGCTGTGTTATATTCCAT
AGTATGCATTACTCAACAAACTGTTGTGCTATTGGATACTTAGGTGGTTTCTTCACTGA
CAATACTGAATAAACATCTCACCGGAATTC

Figure 86

MFLSILVALCLWLHLALGVRGAPCEAVRIPMCRHMPWNITRMPNHLHHSTQENAILAIEQY
EELVDVNCSAVLRFFLCAMYAPICTLEFLHDPIKPCKSVCQRARDDCEPLMKMYNHSWPE
SLACDELPVYDRGVCISPEAIVTDLPEDVKWIDITPDMMVQERPLDVDCKRLSPDRCKCKK
VKPTLATYLSKNYSYVIHAKIKAVQRSGCNEVTTVVDVKEIFKSSSPIPRTQVPLITNSSCQC
PHILPHQDVLIMCYEWRSRMMLLENCLVEKWRDQLSKRSIQWEERLQEQRRTVQDKKKT
AGRTSRSNPPKPKGKPPAPKPASPKKNIKTRSAQKRTNPKRV

Figure 87

AAGCTTGATATCGAATTCGCGGCCGCGTCGACGGGAGGCGCCAGGATCAGTCGGGGCA
CCCGCAGCGCAGGCTGCCACCCACCTGGGCGACCTCCGCGGCGGCGGCGGCGGCT
GGGTAGAGTCAGGGCCGGGGGCGCACGCCGGAACACCTGGGCCGCCGGGCACCGAGC
GTCGGGGGGCTGCGCGGCGCGACCCTGGAGAGGGCGCAGCCGATGCGGGCGGCGGCG
GCGGCGGGGGGCGTGCGGACGGCCGCGCTGGCGCTGCTGCTGGGGGCGCTGCACTGG
GCGCCGGCGCGCTGCGAGGAGTACGACTACTATGGCTGGCAGGCCGAGCCGCTGCACG
GCCGCTCCTACTCCAAGCCGCCGCAGTGCCTTGACATCCCTGCCGACCTGCCGCTCTGC
CACACGGTGGGCTACAAGCGCATGCGGCTGCCCAACCTGCTGGAGCACGAGAGCCTGG
CCGAAGTGAAGCAGCAGGCGAGCAGCTGGCTGCCGCTGCTGGCCAAGCGCTGCCACTC
GGATACGCAGGTCTTCCTGTGCTCGCTCTTTGCGCCCGTCTGTCTCGACCGGCCCATCT
ACCCGTGCCGCTCGCTGTGCGAGGCCGTGCGCGCCGGCTGCGCGCCGCTCATGGAGGC
CTACGGCTTCCCCTGGCCTGAGATGCTGCACTGCCACAAGTTCCCCCTGGACAACGACC
TCTGCATCGCCGTGCAGTTCGGGCACCTGCCCGCCACCGCGCCTCCAGTGACCAAGATC
TGCGCCCAGTGTGAGATGGAGCACAGTGCTGACGGCCTCATGGAGCAGATGTGCTCCA
GTGACTTTGTGGTCAAAATGCGCATCAAGGAGATCAAGATAGAGAATGGGGACCGGA
AGCTGATTGGAGCCCAGAAAAAGAAGAAGCTGCTCAAGCCGGGCCCCCTGAAGCGCA
AGGACACCAAGCGGCTGGTGCTGCACATGAAGAATGGCGCGGGCTGCCCCTGCCCACA
GCTGGACAGCCTGGCGGGCAGCTTCCTGGTCATGGGCCGCAAAGTGGATGGACAGCTG
CTGCTCATGGCCGTCTACCGCTGGGACAAGAAGAATAAGGAGATGAAGTTTGCAGTCA
AATTCATGTTCTCCTACCCCTGCTCCCTCTACTACCCTTTCTTCTACGGGGCGGCAGAGC
CCCACTGAAGGGCACTCCTCCTTGCCCTGCCAGCTGTGCCTTGCTTGCCCTCTGGCCCC
GCCCCAACTTCCAGGCTGACCCGGCCCTACTGGAGGGTGTTTTCACGAATGTTGTTACT
GGCACAAGGCCTAAGGGATGGGCACGGAGCCCAGGCTGTCCTTTTTGACCCAGGGGTC
CTGGGGTCCCTGGGATGTTGGGCTTCCTCTCTCAGGAGCAGGGCTTCTTCATCTGGGTG
AAGACCTCAGGGTCTCAGAAAGTAGGCAGGGGAGGAGAGGGTAAGGGAAAGGTGGAG
GGGCTCAGGGCACCCTGAGGCGGAGGTTTCAGAGTAGAAGGTGATGTCAGCTCCAGCT
CCCCTCTGTCGGTGGTGGGGCCTCACCTTGAAGAGGGAAGTCTCAATATTAGGCTAAG
CTATTTGGGAAAGTTCTCCCCACCGCCCCTGTACGCGTCATCCTAGCCCCCCTTAGGAA
AGGAGTTAGGGTCTCAGTGCCTCCAGCCACACCCCCTGCCTTCCCCAGCTTGCCCATTT
CCCTGCCCCAAGGCCCAGAGCTCCCCCCAGACTGGAGAGCAAGCCCAGCCCAGCCTCG
GGATAGACCCCCTTCTGGTCCGCCCGTGGCTCGATTCCCGGGATTCATTCCTCAGCCTC

TGCTTCTCCCTTTTATCCCAATAAGTTATTGCTACTGCTGTGAGGCCATAGGTACTAGAC
AACCAATACATGCAGGGTTGGGTTTCTAATTTTTTAACTTTTTAATTAAATCAAAGGT
CGACGCGCGGCCGCGGAATTCCTGCAGCCCGGGGGATCCCCGGGTACCGAGCTCGAAT
TC

Figure 88

TEILPALCVLIHHTDVNILVDTVWALSYLTDAGNEQIQMVIDSGIVPHLVPLLSHQEVKVQT
AALRAVGNIVTGTDEQTQVVLNCDALSHFPALLTHPKEKINKEAVWFLSNITAGNQQQVQ
AVIDANLVPMIIHLLDKGDFGTQKEAAWAISNLTISGRKDQVAYLIQQNVIPPFCNLLTVKD
AQVVQVVLDGLSNILKMAEDEAETIGNLIEECGGLEKIEQLQNHENEDIYKLAYEIIDQFFSS
DDIDEDPSLVPEAIQGGTFGFNSSANVPTEGFQF

Figure 89

ATGCATCTCCTCTTATTTCAGCTGCTGGTACTCCTGCCTCTAGGAAAGACCACACGGCA
CCAGGATGGCCGCCAGAATCAGAGTTCTCTTTCCCCCGTACTCCTGCCAAGGAATCAA
AGAGAGCTTCCCACAGGCAACCATGAGGAAGCTGAGGAGAAGCCAGATCTGTTTGTCG
CAGTGCCACACCTTGTAGCCACCAGCCCTGCAGGGGAAGGCCAGAGGCAGAGAGAGA
AGATGCTGTCCAGATTTGGCAGGTTCTGGAAGAAGCCTGAGAGAGAAATGCATCCATC
CAGGGACTCAGATAGTGAGCCCTTCCCACCTGGGACCCAGTCCCTCATCCAGCCGATA
GATGGAATGAAAATGGAGAAATCTCCTCTTCGGGAAGAAGCCAAGAAATTCTGGCACC
ACTTCATGTTCAGAAAAACTCCGGCTTCTCAGGGGGTCATCTTGCCCATCAAAAGCCAT
GAAGTACATTGGGAGACCTGCAGGACAGTGCCCTTCAGCCAGACTATAACCCACGAAG
GCTGTGAAAAAGTAGTTGTTCAGAACAACCTTTGCTTTGGGAAATGCGGGTCTGTTCAT
TTTCCTGGAGCCGCGCAGCACTCCCATACCTCCTGCTCTCACTGTTTGCCTGCCAAGTTC
ACCACGATGCACTTGCCACTGAACTGCACTGAACTTTCCTCCGTGATCAAGGTGGTGAT
GCTGGTGGAGGAGTGCCAGTGCAAGGTGAAGACGGAGCATGAAGATGGACACATCCT
ACATGCTGGCTCCCAGGATTCCTTTATCCCAGGAGTTTCAGCTTGA

Figure 90

MHLLLFQLLVLLPLGKTTRHQDGRQNQSSLSPVLLPRNQRELPTGNHEEAEEKPDLFVAVP
HLVATSPAGEGQRQREKMLSRFGRFWKKPEREMHPSRDSDSEPFPPGTQSLIQPIDGMKME
KSPLREEAKKFWHHFMFRKTPASQGVILPIKSHEVHWETCRTVPFSQTITHEGCEKVVVQN
NLCFGKCGSVHFPGAAQHSHTSCSHCLPAKFTTMHLPLNCTELSSVIKVVMLVEECQCKV
KTEHEDGHILHAGSQDSFIPGVSA

Figure 91

CGGCACGGTTTCGTGGGGACCCAGGCTTGCAAAGTGACGGTCATTTTCTCTTTCTTTCT
CCCTCTTGAGTCCTTCTGAGATGATGGCTCTGGGCGCAGCGGGAGCTACCCGGGTCTTT
GTCGCGATGGTAGCGGCGGCTCTCGGCGGCCACCCTCTGCTGGGAGTGAGCGCCACCT
TGAACTCGGTTCTCAATTCCAACGCTATCAAGAACCTGCCCCCACCGCTGGGCGGCGCT
GCGGGGCACCCAGGCTCTGCAGTCAGCGCCGCGCCGGGAATCCTGTACCCGGGCGGGA
ATAAGTACCAGACCATTGACAACTACCAGCCGTACCCGTGCGCAGAGGACGAGGAGTG
CGGCACTGATGAGTACTGCGCTAGTCCCACCCGCGGAGGGGACGCAGGCGTGCAAATC

GGAATTACTGCAAAAATGGAATATGTGTGTCTTCTGATCAAAATCATTTCCGAGGAGA
AATTGAGGAAACCATCACTGAAAGCTTTGGTAATGATCATAGCACCTTGGATGGGTAT
TCCAGAAGAACCACCTTGTCTTCAAAAATGTATCACACCAAAGGACAAGAAGGTTCTG
TTTGTCTCCGGTCATCAGACTGTGCCTCAGGATTGTGTTGTGCTAGACACTTCTGGTCCA
AGATCTGTAAACCTGTCCTGAAAGAAGGTCAAGTGTGTACCAAGCATAGGAGAAAAGG
CTCTCATGGACTAGAAATATTCCAGCGTTGTTACTGTGGAGAAGGTCTGTCTTGCCGGA
TACAGAAAGATCACCATCAAGCCAGTAATTCTTCTAGGCTTCACACTTGTCAGAGACAC
TAAACCAGCTATCCAAATGCAGTGAACTCCTTTTATATAATAGATGCTATGAAAACCTT
TTATGACCTTCATCAACTCAATCCTAAGGATATACAAGTTCTGTGGTTTCAGTTAAGCA
TTCCAATAACACCTTCCAAAAACCTGGAGTGTAAGAGCTTTGTTTCTTTATGGAACTCC
CCTGTGATTGCAGTAAATTACTGTATTGTAAATTCTCAGTGTGGCACTTACCTGTAAAT
GCAATGAAACTTTTAATTATTTTTCTAAAGGTGCTGCACTGCCTATTTTTCCTCTTGTTA
TGTAAATTTTTGTACACATTGATTGTTATCTTGACTGACAAATATTCTATATTGAACTGA
AGTAAATCATTTCAGCTTATAGTTCTTAAAAGCATAACCCTTTACCCCATTTAATTCTAG
AGTCTAGAACGCAAGGATCTCTTGGAATGACAAATGATAGGTACCTAAAATGTAACAT
GAAAATACTAGCTTATTTTCTGAAATGTACTATCTTAATGCTTAAATTATATTTCCCTTT
AGGCTGTGATAGTTTTTGAAATAAAATTTAACATTTAATATCATGAAATGTTATAAGTA
GACAT

Figure 92

MMALGAAGATRVFVAMVAAALGGHPLLGVSATLNSVLNSNAIKNLPPPLGGAAGHPGSA
VSAAPGILYPGGNKYQTIDNYQPYPCAEDEECGTDEYCASPTRGGDAGVQICLACRKRRK
RCMRHAMCCPGNYCKNGICVSSDQNHFRGEIEETITESFGNDHSTLDGYSRRTTLSSKMYH
TKGQEGSVCLRSSDCASGLCCARHFWSKICKPVLKEGQVCTKHRRKGSHGLEIFQRCYCG
EGLSCRIQKDHHQASNSSRLHTCQRH

Figure 93

GCGGGTCTCGCTTGGGTTCCGCTAATTTCTGTCCTGAGGCGTGAGACTGAGTTCATAGG
GTCCTGGGTCCCCGAACCAGGAAGGGTTGAGGGAACACAATCTGCAAGCCCCCGCGAC
CCAAGTGAGGGGCCCCGTGTTGGGGTCCTCCCTCCCTTTGCATTCCCACCCCTCCGGGC
TTTGCGTCTTCCTGGGGACCCCCTCGCCGGGAGATGGCCGCGTTGATGCGGAGCAAGG
ATTCGTCCTGCTGCCTGCTCCTACTGGCCGCGGTGCTGATGGTGGAGAGCTCACAGATC
GGCAGTTCGCGGGCCAAACTCAACTCCATCAAGTCCTCTCTGGGCGGGGAGACGCCTG
GTCAGGCCGCCAATCGATCTGCGGGCATGTACCAAGGACTGGCATTCGGCGGCAGTAA
GAAGGGCAAAAACCTGGGGCAGGCCTACCCTTGTAGCAGTGATAAGGAGTGTGAAGTT
GGGAGGTATTGCCACAGTCCCCACCAAGGATCATCGGCCTGCATGGTGTGTCGGAGAA
AAAAGAAGCGCTGCCACCGAGATGGCATGTGCTGCCCCAGTACCCGCTGCAATAATGG
CATCTGTATCCCAGTTACTGAAAGCATCTTAACCCCTCACATCCCGGCTCTGGATGGTA
CTCGGCACAGAGATCGAAACCACGGTCATTACTCAAACCATGACTTGGGATGGCAGAA
TCTAGGAAGACCACACACTAAGATGTCACATATAAAAGGGCATGAAGGAGACCCCTGC
CTACGATCATCAGACTGCATTGAAGGGTTTTGCTGTGCTCGTCATTTCTGGACCAAAAT
CTGCAAACCAGTGCTCCATCAGGGGGAAGTCTGTACCAAACAACGCAAGAAGGGTTCT
CATGGGCTGGAAATTTTCCAGCGTTGCGACTGTGCGAAGGGCCTGTCTTGCAAAGTATG
GAAAGATGCCACCTACTCCTCCAAAGCCAGACTCCATGTGTGTCAGAAAATTTGATCA
CCATTGAGGAACATCATCAATTGCAGACTGTGAAGTTGTGTATTTAATGCATTATAGCA
TGGTGGAAAATAAGGTTCAGATGCAGAAGAATGGCTAAAATAAGAAACGTGATAAGA
ATATAGATGATCAC

Figure 94

MAALMRSKDSSCCLLLLAAVLMVESSQIGSSRAKLNSIKSSLGGETPGQAANRSAGMYQG
LAFGGSKKGKNLGQAYPCSSDKECEVGRYCHSPHQGSSACMVCRRKKKRCHRDGMCCPS
TRCNNGICIPVTESILTPHIPALDGTRHRDRNHGHYSNHDLGWQNLGRPHTKMSHIKGHEG
DPCLRSSDCIEGFCCARHFWTKICKPVLHQGEVCTKQRKKGSHGLEIFQRCDCAKGLSCKV
WKDATYSSKARLHVCQKI

Figure 95

CTATCACAATGAGACCAACACAGACACGAAGGTTGGAAATAATACCATCCATGTGCAC
CGAGAAATTCACAAGATAACCAACAACCAGACTGGACAAATGGTCTTTCAGAGACAG
TTATCACATCTGTGGGAGACGAAGAAGGCAGAAGGAGCCACGAGTGCATCATCGACG
AGGACTGTGGGCCCAGCATGTACTGCCAGTTTGCCAGCTTCCAGTACACCTGCCAGCC
ATGCCGGGGCCAGAGGATGCTCTGCACCCGGGACAGTGAGTGCTGTGGAGACCAGCTG
TGTGTCTGGGGTCACTGCACCAAAATGGCCACCAGGGGCAGCAATGGGACCATCTGTG
ACAACCAGAGGGACTGCCAGCCGGGGCTGTGCTGTGCCTTCCAGAGAGGCCTGCTGTT
CCCTGTGTGCACACCCCTGCCCGTGGAGGGCGAGCTTTGCCATGACCCCGCCAGCCGG
CTTCTGGACCTCATCACCTGGGAGCTAGAGCCTGATGGAGCCTTGGACCGATGCCCTTG
TGCCAGTGGCCTCCTCTGCCAGCCCCACAGCCACAGCCTGGTGTATGTGTGCAAGCCG
ACCTTCGTGGGGAGCCGTGACCAAGATGGGGAGATCCTGCTGCCCAGAGAGGTCCCCG
ATGAGTATGAAGTTGGCAGCTTCATGGAGGAGGTGCGCCAGGAGCTGGAGGACCTGGA
GAGGAGCCTGACTGAAGAGATGGCGCTGGGGGAGCCTGCGGCTGCCGCCGCTGCACTG
CTGGGAGGGGAAGAGATTTAGATCTGGACCAGGCTGTGGGTAGATGTGCAATAGAAAT
AGCTAATTTATTTCCCCAGGTGTGTGCTTTAGGCGTGGGCTGACCAGGCTTCTTCCTAC
ATCTTCTTCCCAGTAAGTTTCCCCTCTGGCTTGACAGCATGAGGTGTTGTGCATTTGTTC
AGCTCCCCCAGGCTGTTCTCCAGGCTTCACAGTCTGGTGCTTGGGAGAGTCAGGCAGG
GTTAAACTGCAGGAGCAGTTTGCCACCCCTGTCCAGATTATTGGCTGCTTTGCCTCTAC
CAGTTGGCAGACAGCCGTTTGTTCTACATGGCTTTGATAATTGTTTGAGGGGAGGAGAT
GGAAACAATGTGGAGTCTCCCTCTGATTGGTTTTGGGGAAATGTGGAGAAGAGTGCCC
TGCTTTGCAAACATCAACCTGGCAAAAATGCAACAAATGAATTTTCCACGCAGTTCTTT
CCATGGGCATAGGTAAGCTGTGCCTTCAGCTGTTGCAGATGAAATGTTCTGTTCACCCT
GCATTACATGTGTTTATTCATCCAGCAGTGTTGCTCAGCTCCTACCTCTGTGCCAGGGC
AGCATTTTCATATCCAAGATCAATTCCCTCTCTCAGCACAGCCTGGGGAGGGGGTCATT
GTTCTCCTCGTCCATCAGGGATCTCAGAGGNCTCAGAGACTGCAAGCTGCTTGCCCAA
GTCACACAGCTAGTGAAGACCAGAGCAGTTTCATCTGGTTGTGACTCTAAGCTCAGTGC
TCTCTCCACTACCCCACACCAGCCTTGGTGCCACCAAAAGTGCTCCCCAAAAGGAAGG
AGAATGGGATTTTTCTTTTGAGGCATGCACATCTGGAATTAAGGTCAAACTAATTCTCA
CATCCCTCTAAAAGTAAACTACTGTTAGGAACAGCAGTGTTCTCACAGTGTGGGGCAG
CCGTCCTTCTAATGAAGACAATGATATTGACACTGTCCCTCTTTGGCAGTTGCATTAGT
AACTTTGAAAGGTATATGACTGAGCGTAGCATACAGGTTAACCTGCAGAAACAGTACT
TAGGTAATTGTAGGGCGAGGATTATAAATGAAATTTGCAAAATCACTTAGCAGCAACT
GAAGACAATTATCAACCACGTGGAGAAAATCAAACCGAGCAGGGCTGTGTGAAACAT
GGTTGTAATATGCGACTGCGAACACTGAACTCTACGCCACTCCACAAATGATGTTTTCA
GGTGTCATGGACTGTTGCCACCATGTATTCATCCAGAGTTCTTAAAGTTTAAAGTTGCA
CATGATTGTATAAGCATGCTTTCTTTGAGTTTTAAATTATGTATAAACATAAGTTGCATT
TAGAAATCAAGCATAAATCAC

Figure 96

MQRLGATLLCLLLAAAVPTAPAPAPTATSAPVKPGPALSYPQEEATLNEMFREVEELMEDT
QHKLRSAVEEMEAEEAAAKASSEVNLANLPPSYHNETNTDTKVGNNTIHVHREIHKITNNQ
TGQMVFSETVITSVGDEEGRRSHECIIDEDCGPSMYCQFASFQYTCQPCRGQRMLCTRDSE
CCGDQLCVWGHCTKMATRGSNGTICDNQRDCQPGLCCAFQRGLLFPVCTPLPVEGELCHD
PASRLLDLITWELEPDGALDRCPCASGLLCQPHSHSLVYVCKPTFVGSRDQDGEILLPREVP
DEYEVGSFMEEVRQELEDLERSLTEEMALGEPAAAAAALLGGEEI

Figure 97

AGACGACGTGCTGAGCTGCCAGCTTAGTGGAAGCTCTGCTCTGGGTGGAGAGCAGCCT
CGCTTTGGTGACGCACAGTGCTGGGACCCTCCAGGAGCCCCGGGATTGAAGGATGGTG
GCGGCCGTCCTGCTGGGGCTGAGCTGGCTCTGCTCTCCCCTGGGAGCTCTGGTCCTGGA
CTTCAACAACATCAGGAGCTCTGCTGACCTGCATGGGGCCCGGAAGGGCTCACAGTGC
CTGTCTGACACGGACTGCAATACCAGAAAGTTCTGCCTCCAGCCCCGCGATGAGAAGC
CGTTCTGTGCTACATGTCGTGGGTTGCGGAGGAGGTGCCAGCGAGATGCCATGTGCTG
CCCTGGGACACTCTGTGTGAACGATGTTTGTACTACGATGGAAGATGCAACCCCAATAT
TAGAAAGGCAGCTTGATGAGCAAGATGGCACACATGCAGAAGGAACAACTGGGCACC
CAGTCCAGGAAAACCAACCCAAAAGGAAGCCAAGTATTAAGAAATCACAAGGCAGGA
AGGGACAAGAGGGAGAAAGTTGTCTGAGAACTTTTGACTGTGGCCCTGGACTTTGCTG
TGCTCGTCATTTTTGGACGAAAATTTGTAAGCCAGTCCTTTTGGAGGGACAGGTCTGCT
CCAGAAGAGGGCATAAAGACACTGCTCAAGCTCCAGAAATCTTCCAGCGTTGCGACTG
TGGCCCTGGACTACTGTGTCGAAGCCAATTGACCAGCAATCGGCAGCATGCTCGATTA
AGAGTATGCCAAAAAATAGAAAAGCTATAAATATTTCAAAATAAAGAAGAATCCACAT
TGC

Figure 98

MVAAVLLGLSWLCSPLGALVLDFNNIRSSADLHGARKGSQCLSDTDCNTRKFCLQPRDEK
PFCATCRGLRRRCQRDAMCCPGTLCVNDVCTTMEDATPILERQLDEQDGTHAEGTTGHPV
QENQPKRKPSIKKSQGRKGQEGESCLRTFDCGPGLCCARHFWTKICKPVLLEGQVCSRRGH
KDTAQAPEIFQRCDCGPGLLCRSQLTSNRQHARLRVCQKIEKL

Figure 99

AGGCAGAATACTTCTATGAATTCCTGTCCTTGCGCTCCCTGGATAAAGGCATCATGGCA
GATCCAACCGTCAATGTCCCTCTGCTGGGAACAGTGCCTCACAAGGCATCAGTTGTTCA
AGTTGGTTTCCCATGTCTTGGAAAACAGGATGGGGTGGCAGCATTTGAAGTGGATGTG
ATTGTTATGAATTCTGAAGGCAACACCATTCTCCAAACACCTCAAAATGCTATCTTCTT
TAAAACATGTCAACAAGCTGAGTGCCCAGGCGGGTGCCGAAATGGAGGCTTTTGTAAT
GAAAGACGCATCTGCGAGTGTCCTGATGGGTTCCACGGACCTCACTGTGAGAAAGCCC
TTTGTACCCCACGATGTATGAATGGTGGACTTTGTGTGACTCCTGGTTTCTGCATCTGCC
CACCTGGATTCTATGGAGTGAACTGTGACAAAGCAAACTGCTCAACCACCTGCTTTAAT

AGTGTGAAATCAGCAAATGCCCACAACCCTGTCGAAATGGAGGTAAATGCATTGGTAA
AAGCAAATGTAAGTGTTCCAAAGGTTACCAGGGAGACCTCTGTTCAAAGCCTGTCTGC
GAGCCTGGCTGTGGTGCACATGGAACCTGCCATGAACCCAACAAATGCCAATGTCAAG
AAGGTTGGCATGGAAGACACTGCAATAAAAGGTACGAAGCCAGCCTCATACATGCCCT
GAGCGCAGCAGCGCCCAGCTCAGGCAGCACACGCCTTCACTTAAAAAGGCCGAGGAG
CGGCGGCATCCACCTGAATCCAATTACATCTGGTGAACTCCGACATCTGAAACGTTTTA
AGTTACACCAAGTTCATAGCCTTTGTTAACCTTTCATGTGTTGAATGTTCAAATAATGTT
CATTACACTTAAGAATACTGGCCTGAATTTTATTAGCTTCATTATAAATCACTGAGCTG
ATATTTACTCTTCCTTTTAAGTTTTCTAAGTACGTCTGTAGCATGATGGTATAGATTTTC
TTGTTTCAGTGCTTTGGGACAGATTTTATATTATGTCAATTGATCAGGTTAAAATTTTCA
GTGTGTAGTTGGCAGATATTTTCAAAATTACAATGCATTTATGGTGTCTGGGGGCAGGG
GAACATCAGAAAGGTTAAATTGGGCAAAAATGCGTAAGTCACAAGAATTTGGATGGTG
CAGTTAATGTTGAAGTTACAGCATTTCAGATTTTATTGTCAGATATTTAGATGTTTGTTA
CATTTTTAAAAATTGCTCTTAATTTTTAAACTCTCAATACAATATATTTTGACCTTACCA
TTATTCCAGAGATTCAGTATTAAAAAAAAAAAAATTACACTGTGGTAGTGGCATTTAA
ACAATATAATATATTCTAAACACAATGAAATAGGGAATATAATGTATGAACTTTTTGCA
TTGGCTTGAAGCAATATAATATATTGTAAACAAAACACAGCTCTTACCTAATAAACATT
TTATACTGTTTGTATGTATAAAATAAAGGTGCTGCTTTAGTTTTC

Figure 100

MARRSAFPAAALWLWSILLCLLALRAEAGPPQEESLYLWIDAHQARVLIGFEEDILIVSEGK
MAPFTHDFRKAQQRMPAIPVNIHSMNFTWQAAGQAEYFYEFLSLRSLDKGIMADPTVNVP
LLGTVPHKASVVQVGFPCLGKQDGVAAFEVDVIVMNSEGNTILQTPQNAIFFKTCLQAECP
GGCRNGGFCNERRICECPDGFHGPHCEKALCTPRCMNGGLCVTPGFCICPPGFYGVNCDK
ANCSTTCFNGGTCFYPGKCICPPGLEGEQCEISKCPQPCRNGGKCIGKSKCKCSKGYQGDL
CSKPVCEPGCGAHGTCHEPNKCQCQEGWHGRHCNKRYEASLIHALR
PAGAQLRQHTPSLKKAEERRDPPESNYIW

Figure 101

ATGGGCATCGGGCGCAGCGAGGGGGGCCGCCGCGGGGCAGCCCTGGGCGTGCTGCTG
GCGCTGGGCGCGGCGCTTCTGGCCGTGGGCTCGGCCAGCGAGTACGACTACGTGAGCT
TCCAGTCGGACATCGGCCCGTACCAGAGCGGGCGCTTCTACACCAAGCCACCTCAGTG
CGTGGACATCCCCGCGGACCTGCGGCTGTGCCACAACGTGGGCTACAAGAAGATGGTG
CTGCCCAACCTGCTGGAGCACGAGACCATGGCGGAGGTGAAGCAGCAGGCCAGCAGC
TGGGTGCCCCTGCTCAACAAGAACTGCCACGCCGGCACCCAGGTCTTCCTCTGCTCGCT
CTTCGCGCCCGTCTGCCTGGACCGGCCCATCTACCCGTGTCGCTGGCTCTGCGAGGCCG
TGCGCGACTCGTGCGAGCCGGTCATGCAGTTCTTCGGCTTCTACTGGCCCGAGATGCTT
AAGTGTGACAAGTTCCCCGAGGGGGACGTCTGCATCGCCATGACGCCGCCCAATGCCA
CCGAAGCCTCCAAGCCCCAAGGCACAACGGTGTGTCCTCCCTGTGACAACGAGTTGAA
ATCTGAGGCCATCATTGAACATCTCTGTGCCAGCGAGTTTGGGCTGAGTTTAAAGATGA
TTGTGGGTAGCTCCCATAACTCATGCTGCACGCTGGGTCCTTCTCATCCCAACTCCTCA
AAGCGGCAGGAGCAGGAACTGGGGACTCCTGAGAGAAGGCTTGGATATGGCCTTTTAT
TACACTTCATCCAAGGAAATCTGCCCCCACCCTGTGCCCAGGCCCGATCACGCATGAG
GCTAAAGACGGAGGCCACTCCGCTGGCTCTGGGTAGATCTGCCCCTGGACTGTTTGCC
GACTGCCCGGAGCGCCCTCTGCCGGTCTGCAGCTTCCCACACCACACGGAAGAAGTGG
GGAAACTGAGGATACATTCTTTCCTCCTCCAGGTAAAGGGATTCTCAATGAAGGGCTTG
TGTGCACCTTCCACACTTAGATACCTCTACTACCTGAAAACCAGCATGCAGCATGTACA
TCAAGAGTACCAGGCACATAGTGCTCAAGTCTGGGCTAATATGCCACCTGCAGAGAGA
TGTAAAGATGAAGAAGACAAAGCCATGTTTTCAAAGTGA

Figure 102

MGIGRSEGGRRGAALGVLLALGAALLAVGSASEYDYVSFQSDIGPYQSGRFYTKPPQCVDI
PADLRLCHNVGYKKMVLPNLLEHETMAEVKQQASSWVPLLNKNCHAGTQVFLCSLFAPV
CLDRPIYPCRWLCEAVRDSCEPVMQFFGFYWPEMLKCDKFPEGDVCIAMTPPNATEASKP
QGTTVCPPCDNELKSEAIIEHLCASEFGLSLKMIVGSSHNSCCTLGPSHPNSSKRQEQELGTP
ERRLGYGLLLHFIQGNLPPPCAQARSRMRLKTEATPLALGRSAPGLFADCPERPLPVCSFPH
HTEEVGKLRIHSFLLQVKGFSMKGLCAPSTLRYLYYLKTSMQHVHQEYQAHSAQVWANM
PPAERCKDEEDKAMFSK

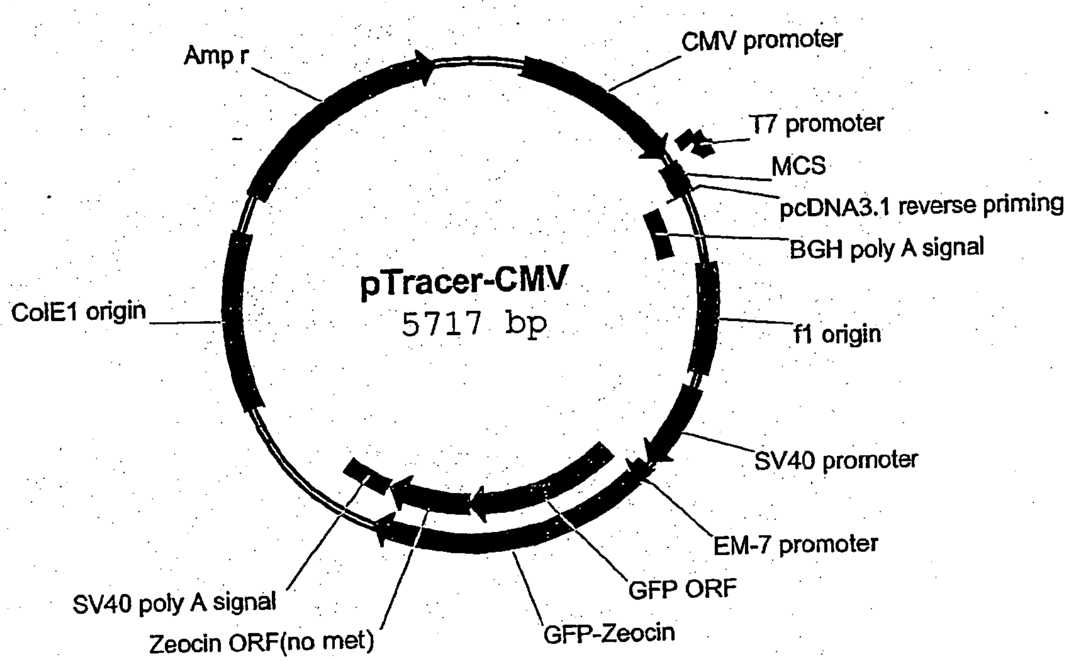
Figure 103

GGCGGGTTCGCGCCCCGAAGGCTGAGAGCTGGCGCTGCTCGTGCCCTGTGTGCCAGAC
GGCGGAGCTCCGCGGCCGGACCCCGCGGCCCCGCTTTGCTGCCGACTGGAGTTTGGGG
GAAGAAACTCTCCTGCGCCCCAGAAGATTTCTTCCTCGGCGAAGGGACAGCGAAAGAT
GAGGGTGGCAGGAAGAGAAGGCGCTTTCTGTCTGCCGGGGTCGCAGCGCGAGAGGGC
AGTGCCATGTTCCTCTCCATCCTAGTGGCGCTGTGCCTGTGGCTGCACCTGGCGCTGGG
CGTGCGCGGCGCGCCCTGCGAGGCGGTGCGCATCCCTATGTGCCGGCACATGCCCTGG
AACATCACGCGGATGCCCAACCACCTGCACCACAGCACGCAGGAGAACGCCATCCTGG
CCATCGAGCAGTACGAGGAGCTGGTGGACGTGAACTGCAGCGCCGTGCTGCGCTTCTT
CTTCTGTGCCATGTACGCGCCCATTTGCACCCTGGAGTTCCTGCACGACCCTATCAAGC
CGTGCAAGTCGGTGTGCCAACGCGCGCGCGACGACTGCGAGCCCCTCATGAAGATGTA
CAACCACAGCTGGCCCGAAAGCCTGGCCTGCGACGAGCTGCCTGTCTATGACCGTGGC
GTGTGCATTTCGCCTGAAGCCATCGTCACGGACCTCCCGGAGGATGTTAGTGGATAGA
CATCACACCAGACATGATGGTACAGGAAAGGCCTCTTGATGTTGACTGTAAACGCCTA
AGCCCCGATCGGTGCAAGTGTAAAAAGGTGAAGCCAACTTTGGCAACGTATCTCAGCA
AAAACTACAGCTATGTTATTCATGCCAAAATAAAAGCTGTGCAGAGGAGTGGCTGCAA
TGAGGTCACAACGGTGGTGGATGTAAAAGAGATCTTCAAGTCCTCATCACCCATCCCTC
GAACTCAAGTCCCGCTCATTACAAATTCTTCTTGCCAGTGTCCACACATCCTGCCCCAT
CAAGATGTTCTCATCATGTGTTACGAGTGGCGTTCAAGGATGATGCTTCTTGAAAATTG
CTTAGTTGAAAAATGGAGAGATCAGCTTAGTAAAAGATCCATACAGTGGGAAGAGAG
GCTGCAGGAACAGCGGAGAACAGTTCAGGACAAGAAGAAAACAGCCGGGCGCACCAG
TCGTAGTAATCCCCCCAAACCAAAGGGAAAGCCTCCTGCTCCCAAACCAGCCAGTCCC
AAGAAGAACATTAAAACTAGGAGTGCCCAGAAGAGAACAAACCCGAAAAGAGTGTGA
GCTAACTAGTTTCCAAAGCGGAGACTTCCGACTTCCTTACAGGATGAGGCTGGGCATTG
CCTGGGACAGCCTATGTAAGGCCATGTGCCCCTTGCCCTAACAACTCACTGCAGTGCTC
TTCATAGACACATCTTGCAGCATTTTTCTTAAGGCTATGCTTCAGTTTTTCTTTGTAAGC
CATCACAAGCCATAGTGGTAGGTTTGCCCTTTGGTACAGAAGGTGAGTTAAAGCTGGT
GGAAAAGGCTTATTGCATTGCATTCAGAGTAACCTGTGTGCATACTCTAGAAGAGTAG
GGAAAATAATGCTTGTTACAATTCGACCTAATATGTGCATTGTAAAATAAATGCCATAT
TTCAAACAAAACACGTAATTTTTTTACAGTATGTTTTATTACCTTTTGATATCTGTTGTT
GCAATGTTAGTGATGTTTTAAAATGTGATGAAAATATAATGTTTTTAAGAAGGAACAGT
AGTGGAATGAATGTTAAAAGATCTTTATGTGTTTATGGTCTGCAGAAGGATTTTTGTGA
TGAAAGGGGATTTTTTGAAAAATTAGAGAAGTAGCATATGGAAAATTATAATGTGTTT
TTTTACCAATGACTTCAGTTTCTGTTTTTAGCTAGAAACTTAAAAACAAAAATAATAAT
AAAGAAAAATAAATAAAAAGGAGAGGCAGACAATGTCTGGATTCCTGTTTTTTGGTTA

CCTGATTTCCATGATCATGATGCTTCTTGTCAACACCCTCTTAAGCAGCACCAGAAACA
GTGAGTTTGTCTGTACCATTAGGAGTTAGGTACTAATTAGTTGGCTAATGCTCAAGT
ATTTTATACCCACAAGAGAGGTATGTCACTCATCTTACTTCCCAGGACATCCACCCTGA
GAATAATTTGACAAGCTTAAAAATGGCCTTCATGTGAGTGCCAAATTTTGTTTTTCTTC
ATTTAAATATTTTCTTTGCCTAAATACATGTGAGAGGAGTTAAATATAAATGTACAGAG
AGGAAAGTTGAGTTCCACCTCTGAAATGAGAATTACTTGACAGTTGGGATACTTTAATC
AGAAAAAAAGAACTTATTTGCAGCATTTTATCAACAAATTTCATAATTGTGGACAATTG
GAGGCATTTATTTTAAAAAACAATTTTATTGGCCTTTTGCTAACACAGTAAGCATGTAT
TTTATAAGGCATTCAATAAATGCACAACGCCCAAAGGAAATAAAATCCTATCTAATCC
TACTCTCCACTACACAGAGGTAATCACTATTAGTATTTGGCATATTATTCTCCAGGTGT
TTGCTTATGCACTTATAAAATGATTTGAACAAATAAAACTAGGAACCTGTATACATGTG
TTTCATAACCTGCCTCCTTTGCTTGGCCCTTTATTGAGATAAGTTTTCCTGTCAAGAAAG
CAGAAACCATCTCATTTCTAACAGCTGTGTTATATTCCATAGTATGCATTACTCAACAA
ACTGTTGTGCTATTGGATACTTAGGTGGTTTCTTCACTGACAATACTGAATAAACATCT
CACCGGAATTC

Figure 104

MFLSILVALCLWLHLALGVRGAPCEAVRIPMCRHMPWNITRMPNHLHHSTQENAILAIEQY
EELVDVNCSAVLRFFFCAMYAPICTLEFLHDPIKPCKSVCQRARDDCEPLMKMYNHSWPES
LACDELPVYDRGVCISPEAIVTDLPEDVKWIDITPDMMVQERPLDVDCKRLSPDRCKCKKV
KPTLATYLSKNYSYVIHAKIKAVQRSGCNEVTTVVDVKEIFKSSSPIPRTQVPLITNSSCQCP
HILPHQDVLIMCYEWRSRMMLLENCLVEKWRDQLSKRSIQWEERLQEQRRTVQDKKKTA
GRTSRSNPPKPKGKPPAPKPASPKKNIKTRSAQKRTNPKRV



pTracer-CMV
5717 bp
Amp r
CMV promoter
T7 promoter
MCS
pcDNA3.1 reverse priming
BGH poly A signal
f1 origin
SV40 promoter
EM-7 promoter
GFP ORF
GFP-Zeocin
Zeocin ORF(no met)
SV40 poly A signal
ColE1 origin

Figure 105

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Published:
— *with international search report*

(88) Date of publication of the international search report: 24 April 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/077204 A3

(54) Title: STEM CELL DIFFERENTIATION

(57) Abstract: There is provided a method to modulate the differentiation state of embryonic stem cells in culture by the providing

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/01195

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N5/06 C12N15/63

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, EMBL, EPO-Internal, WPI Data, PAJ, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WAKEMAN JANE A ET AL: "Human Wnt-13 is developmentally regulated during the differentiation of NTERA-2 pluripotent human embryonal carcinoma cells." ONCOGENE, vol. 17, no. 2, 16 July 1998 (1998-07-16), pages 179-186, XP002216009 ISSN: 0950-9232 page 184, right-hand column, paragraph 1 ---	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 October 2002	22.01.03

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nichogiannopoulou, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SMOLICH BEVERLY D ET AL: "Regulated expression of Wnt family members during neuroectodermal differentiation of P19 embryonal carcinoma cells: Overexpression of Wnt-1 perturbs normal differentiation-specific properties." DEVELOPMENTAL BIOLOGY, vol. 166, no. 1, 1994, pages 300-310, XP002216010 ISSN: 0012-1606 abstract ---	1
A	LIU TONG ET AL: "Activation of rat Frizzled-1 promotes Wnt signaling and differentiation of mouse F9 teratocarcinoma cells via pathways that require Galphaq and Galphao function." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 274, no. 47, 19 November 1999 (1999-11-19), pages 33539-33544, XP002216011 ISSN: 0021-9258 abstract ---	1
A	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 16 November 2000 (2000-11-16) LAKO MAJLINDA ET AL: "Involvement of Wnt genes in early haematopoiesis and identification of Wnt3 as a regulator of haematopoietic commitment." Database accession no. PREV200100290162 XP002216012 abstract & BLOOD, vol. 96, no. 11 Part 2, 16 November 2000 (2000-11-16), page 133b 42nd Annual Meeting of the American Society of Hematology;San Francisco, California, USA; December 01-05, 2000 ISSN: 0006-4971 ---	1
A	US 5 780 300 A (ARTAVANIS-TSAKONAS SPYRIDON ET AL) 14 July 1998 (1998-07-14) the whole document -----	1

International application No.
PCT/GB 02/01195

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 7, 12, 13, 22-26 all partially, 2 and 4 completely

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

The claims of the present application relate to methods for modulating and/or inhibiting embryonic stem cell differentiation by adding a ligand or a Wnt inhibitor to the culture or by coculture with cells which have been transfected with a nucleic acid encoding such a ligand or such a Wnt inhibitor.

However, the application only discloses the differential gene expression of a limited number of genes upon retinoic acid induced in vitro differentiation of an embryonal carcinoma cell line. No modulation of differentiation of embryonic stem cells is shown by any of the claimed methods.

Hence, the application provides neither support within the meaning of Article 6 PCT nor disclosure within the meaning of Article 5 PCT for any of the claimed subject matter. A meaningful search over the claimed scope is thus impossible.

Consequently, no search has been carried out for the present set of claims.

The applicant's attention is drawn to the fact that the same objection will arise for all the additional, non-unified inventions defined under the non-unity objection raised in the communication pursuant to Article 17(3)(a) PCT.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: Claims 1, 7, 12, 13,
22-26 all partially, 2 and 4 completely

Methods to modulate embryonic stem cell differentiation by providing a ligand to the culture, the ligand being human Wnt13

Inventions 2-23: claims 1, 3, 5-7, 12, 13,
22-26 all partially

As invention 1 the ligand being WNT-1, WNT-2, WNT2B, WNT3, WNT4, WNT5A, WNT6, WNT7A, WNT8B, WNT10B, WNT11, WNT14, WNT16, murine notch ligand delta-like (DLL)1, murine notch ligand jagged (JAG)1, human JAG1, human JAG2, murine JAG2, human DLL3, human DLL1, human DLL4, and murine DLL4 respectively.

Inventions 24-32 : Claims 8, 12-15,
22-26 all partially

Methods to modulate embryonic stem cell differentiation by coculturing with cells transfected with a ligand, the ligand being murine notch ligand delta-like (DLL)1, murine notch ligand jagged (JAG)1, human JAG1, human JAG2, murine JAG2, human DLL3, human DLL1, human DLL4, and murine DLL4 respectively.

Invention 33: Claims 9-11 completely, 12-15,
22-26 all partially

Methods to modulate embryonic stem cell differentiation by coculturing with cells transfected with a ligand, the ligand being human Wnt13.

Inventions 34-57: Claims 16-18, 22,
26 all partially

Methods to inhibit embryonic stem cell differentiation by providing a Wnt inhibitor to the culture, the Wnt inhibitor being frizzled (FZD)1, FZD2, FZE3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, FZD10, frizzled related protein (FRP), SARP1, SARP2, FRZB, FRPHE, SARP3, cerberus (CER)1, dickkopf (DKK)1, DKK2, DKK3, DKK4, Wnt inhibitory factor (WIF)-1, SRFP1, and

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

SRFP4 respectively.

Inventions 58-82: Claims 19-22, 26 all partially

Methods to inhibit embryonic stem cell differentiation by coculturing with cells transfected with a Wnt inhibitor, the Wnt inhibitor being frizzled (FZD)1, FZD2, FZE3, FZD4, FZD5, FZD6, FZD7, FZD8, FZD9, FZD10, frizzled related protein (FRP), SARP1, SARP2, FRZB, FRPHE, SARP3, cerberus (CER)1, dickkopf (DKK)1, DKK2, DKK3, DKK4, Wnt inhibitory factor (WIF)-1, SRFP1, and SRFP4 respectively.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 02/01195

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5780300 A	14-07-1998	AU 732629 B2	26-04-2001
		AU 7264996 A	17-04-1997
		CA 2233534 A1	03-04-1997
		EP 0948348 A1	13-10-1999
		JP 2000511043 T	29-08-2000
		WO 9711716 A1	03-04-1997
		US 6149902 A	21-11-2000